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THE CLINICAL SIGNIFICANCE OF APICAL HEART MURMURS.*

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Introduction. Clinical experience with heart murmurs is a very important phase of the study of their significance. Information derived from examinations of selected or unselected groups of individuals from communities at large adds also to our knowledge of heart murmurs. Such information can be obtained through life insurance, school and college, industrial and routine annual community examinations if they are conducted with care. A statement, however, of the part of the country or world where the data are gathered as well as of the age and social and industrial status may be of considerable importance. For example, in warmer parts of the United States and elsewhere in the world rheumatic valvular disease appears to be far less common than in the more northern states and countries. Also this type of heart disease is more common among the poorer people than among the well-to-do.

It is my purpose now to discuss the clinical significance of apical heart murmurs, especially based on 2500 private patients referred to me because of cardiac symptoms or signs. These cases have been almost exclusively New England residents. 2217 have been analyzed in detail. Experience with cardiac patients in the wards and outpatient department of the Massachusetts General Hospital and during the World War also forms a part of the basis for my discussion. A considerable number of my private patients have been referred to me by life-insurance examiners for opinion as

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to the significance of some sign of cardiovascular nature, but the bulk of the cases I have seen at the request of general practitioners or internists for advice as to cardiovascular symptoms or physical findings.

An analysis of general medical, surgical, or special groups of patients in private or hospital practice would, of course, give results and statistics different from those to be reported here, and also of interest and importance. For good general or special discussions of heart murmurs, I can refer to most of the leading modern textbooks or systems of medicine, and especially to the works of the late Sir James Mackenzie, Austin Flint, Potain, Thayer, and Parmenter.

Apical heart murmurs I shall divide into those that are loudest or localized there and those that are obviously transmitted from the base. Both groups I shall subdivide again into systolic and diastolic murmurs. Very little time need be spent in discussing the murmurs transmitted from the base though it is, of course, important to know that such murmurs can be so transmitted. They can be easily detected by following loud basal murmurs as they decrease in intensity but not in character toward and to the apex.

Apical Systolic Murmurs Transmitted from the Base. Systolic murmurs of aortic stenosis, of aortic dilatation or aneurysm, of pulmonic stenosis, and of rare interventricular septal defects may be transmitted even to the apex but they are generally much less intense there than at the base. Their character is unchanged. One recent extraordinary case of well-marked aortic stenosis and undeformed mitral valve, proved by autopsy at the Massachusetts General Hospital, showed during life a harsh systolic murmur with thrill at the apex, with a relatively slight systolic murmur at the aortic area. Mitral disease had been diagnosed antemortem with no thought of aortic stenosis. This is certainly a very rare exception. Functional pulmonic systolic murmurs are rarely heard at the apex. In my series of 2217 cases which were analyzed up to that number in order to include 1000 cases with apical systolic murmurs not transmitted from the base, there were 50 cases with apical systolic murmurs which were obviously transmitted from the base. Thus the ratio of apical systolic murmurs transmitted and not transmitted from the base was just 1 to 20. A rare case was difficult to interpret.

Apical Diastolic Murmurs Transmitted from the Base. Apical diastolic murmurs transmitted from the base are not rare. Almost invariably they mean well-marked aortic regurgitation. With extreme rarity a diastolic murmur of patent ductus arteriosus or possibly even a Graham-Steell murmur of pulmonic regurgitation or the diastolic murmur of the excessively rare organic pulmonic regurgitation may be transmitted to the apex. Of 100 of my cases of aortic diastolic murmurs, 63 were not heard at the apex and 37 were so heard, 3 loudly, two of these last better there than at the

base, the character and time of the murmur and the full pulse pressure proving the aortic-valve origin of the murmur. Mitral diastolic murmurs may be superimposed on the aortic diastolic murmurs heard at the apex. The difference in time and character of the murmurs permits their differentiation. So-called accidental or respiratory diastolic murmurs over the heart are rare; I do not remember having heard one at the apex.

Apical Systolic Murmurs not Transmitted from the Base. Of the murmurs originating at the apex, those that are systolic in time may or may not be important, those that occur in diastole are always important. Such apical systolic murmurs may be divided into three groups: (1) Those which are slight, often variable and not associated with obvious valvular disease or cardiac dilatation; (2) those due to pathology of the mitral valve or its attachments, and (3) those due to mitral insufficiency resulting from dilatation of the left heart chambers. Valvular disease and cardiac dilatation may coëxist, as in some rheumatic cases in particular. It is then impossible to determine how much of the murmur is due to the dilatation and how much to the valve damage. Also sometimes when the murmur is very slight or absent, valvular disease or dilatation may be present but the bloodflow insufficient or the mitral regurgitation too extreme to cause a murmur.

I have analyzed 1000 of my cases showing apical systolic murmurs not transmitted from the base into slight, moderate and marked murmurs, and I shall present the figures of this analysis as I discuss these subdivisions.

I. **Slight Apical Systolic Murmurs.** Slight apical systolic murmurs not transmitted from the base are common and of themselves of little or no importance in the absence of other signs of heart trouble. Their mechanism is often obscure. Sometimes they are the result of the rushing of air into the lung borders near the heart when systole sharply diminishes the heart size. Such murmurs are apt to change with change in position or with phase of respiration, often disappearing under certain conditions. They are slight and negligible. Sometimes slight apical systolic murmurs may perhaps be normal variations due to congenitally ill-fitting or ill-closing valve cusps, varying somewhat with intracardiac pressure changes and also probably with position, respiration and heart rate and filling. Of my 1000 cases with apical systolic murmurs 490 were slight in degree and of these 176 had apparently normal hearts, although a considerable number complained of symptoms of effort syndrome or showed irritability by the presence of premature beats. One was examined during a paroxysm of tachycardia, 7 during infectious diseases and 8 others were exhausted for one reason or another. There were 38 cases that could not be classified as either normal or diseased, and 276 that were thought to have organic heart disease. Thus of the series of 490 cases with slight apical systolic murmurs 56 per

cent had definite heart disease so far as I could tell by various methods of examination. Of course, this percentage is far higher than would be found in people with slight apical systolic murmurs picked up in the community at large. It is, however, significant. Many of the organic cases showed other murmurs such as mitral or aortic diastolic murmurs and practically all showed some cardiac enlargement. Of the 276 cases with slight apical systolic murmurs and probable organic heart disease, 33 were definitely rheumatic in origin, and 24 probably rheumatic but without a clear history. Almost all of these 57 "rheumatic type" cases showed mitral diastolic murmurs as well as systolic, and so were considered to have valvular disease. Dilatation due to the rheumatic cardiac involvement may have been a factor however.

Of the 218 cases in which dilatation was probably the chief factor, hypertension alone was present in 35; hypertension and uremia in 2; apparently both hypertension and arteriosclerosis in 44; arteriosclerosis, sometimes perhaps with hypertension in the past but no longer present, 96; thyroid cardiac involvement, 5; dilatation due to aortic regurgitation, 5; luetic cardiac involvement without aortic regurgitation, 3; angina pectoris alone, 16; and unknown factors, 12. There was one case of evident congenital heart disease. Often the bigger and weaker the heart, the less intense the mitral systolic murmur becomes. Thus a very large failing heart, with gallop rhythm perhaps but no murmurs, may have extensive mitral dilatation while a much smaller, less exhausted heart may give a loud mitral systolic murmur with far less dilatation.

Loud mitral systolic murmurs are always important even though they may be only temporary indications of ill health as from dilatation due to loss of tone in anemia or infectious disease. They are more important than functional pulmonic systolic murmurs, which are commoner and produced in most normal people by forced expiration in the recumbent position. The intensity and character of the loud apical systolic murmur do not distinguish between the two causes, namely, valvular disease and cardiac dilatation. The rougher systolic murmurs, especially those with thrills, are usually found, however, when the valves are damaged. Transmission of the mitral systolic murmur to axilla and back depends, as a rule, simply on its intensity. The etiologic factors behind mitral valvular disease are most commonly rheumatic endocarditis, less commonly other types of endocarditis, and least often arteriosclerotic change. The etiologic factors behind cardiac dilatation due to heart disease, are coronary disease, hypertension, adhesive pericarditis, anemia, and failure from any cause (as in some cases of rheumatic pancarditis). Cardiorespiratory murmurs are rarely if ever loud at the apex.

II. **Moderately Loud Apical Systolic Murmurs.** In my series of 1000 cases showing apical systolic murmurs not transmitted from the

base, 490 in which the murmur was slight in degree have already been analyzed. Two hundred and forty of the remaining 510 showed murmurs of moderate intensity and 270 very loud murmurs. Of the 240 moderate murmur cases, only 12 were thought to have normal hearts. Of these 12, 2 had anemia, 2 infectious disease and 2 exhaustion at the time of examination. Twenty-one more were doubtful. In them I could not tell whether the heart was diseased or not. The remaining 207 of the 240 (or 86 per cent) appeared to have definite organic heart disease. Of these 207, 90 were of the rheumatic type, 68 with, and 22 without, rheumatic history. Two were cases of subacute bacterial endocarditis. The remaining 115 patients, except for 3 with congenital heart disease, appeared to have moderately loud apical systolic murmurs due mainly to cardiac dilatation, although it is often difficult in the arteriosclerotic cases to know when actual sclerotic valve deformity may be present as an associated or primary factor. Hypertension was present in 16, arteriosclerosis without hypertension in 30, hypertension with probable arteriosclerosis in 27, aortic regurgitation in 14, luetic heart disease without aortic regurgitation in 5, angina pectoris in 5 and unknown factors in 15.

III. **Very Loud Apical Systolic Murmurs.** Of the 270 cases with very loud apical systolic murmurs not transmitted from the base, only two were thought to have normal hearts and one of these was anemic. In 4 it was not known whether the heart was diseased or not, and in the remaining 264 (or 98 per cent), organic heart disease was believed to be present. Of these 264, 148 were diagnosed "rheumatic" in type, 100 with definite history of rheumatic infection and 48 without. One was a case of subacute bacterial endocarditis. Three were congenital. The remaining 112 I thought were cases primarily of cardiac dilatation although here again arteriosclerotic valve deformity may have accounted for a few cases. Of the 112 cases, 3 had hypertension alone, 2 hypertension and uremia, 37 arteriosclerosis chiefly, 30 hypertension and probable arteriosclerosis, 2 hyperthyroidism, 3 adherent pericarditis, 9 aortic regurgitation, 4 luetic heart disease without aortic regurgitation, 6 angina pectoris, and 16 unknown factors.

Of the total 1000 cases, 298 showed probably primarily valvular disease, 295 rheumatic in type, 201 with a definite history of a rheumatic infection, and 3 subacute bacterial. In addition to these 295 cases with rheumatic mitral systolic murmurs, there were in the whole series 70 other cases of rheumatic mitral disease with mitral diastolic murmurs but no mitral systolic murmurs. Thus out of 365 patients with rheumatic mitral disease 70 (or 19 per cent) showed only mitral diastolic murmurs. Such murmurs often accompanied the mitral systolic murmurs in the other cases. Among the 1000 cases there was also a total of 159 cases of hypertension, 54 uncomplicated, 4 with uremia and 101 with probable arteriosclerosis.

Two hundred and sixty-four appeared to have coronary disease (excluding uncomplicated angina pectoris), and of these 101 had also hypertension at the time of examination (and are included in the figures above). There were 7 cases of hyperthyroid heart disease altogether and 3 cases with adhesive pericarditis. Twenty-eight patients had aortic regurgitation primarily, and 8 more luetic aortitis without this valve lesion. Twenty-seven cases showed uncomplicated angina pectoris, 7 congenital heart disease, and in 43 the pathology was not known.

A total of 190 out of the 1000 cases seemed to have normal hearts (only 19 per cent) and of these 9 had infectious disease, 3 anemia, 10 exhaustion and 1 paroxysmal tachycardia. In 63 cases it was not known whether heart disease was present or not.

Prognosis of Organic Mitral Systolic Murmurs. The organic mitral systolic murmur, even the very loudest, is compatible with a long active life but usually it is a sign of important heart disease when found clinically. Temporarily its presence need not prevent the demonstration of vigorous cardiovascular and general strength as indicated, for example, by various functional tests, but eventually it usually represents trouble which limits both duration of life and activity. The louder the murmur the worse the prognosis. In my own series of 270 cases with very loud mitral systolic murmurs, 75 (or 28 per cent) have died within a very few years of the finding of the murmur, of the 240 cases with moderate mitral systolic murmurs 41 (or 17 per cent) have died, while 47 (or only 9.6 per cent) of the 490 cases with slight systolic murmurs have died. All but 2 of the cases with slight systolic murmurs who have died had been diagnosed as having definite heart disease.

Heart Disease without Apical Systolic Murmurs. The absence of an apical systolic murmur by no means rules out heart disease. During the same length of time (several years) when I encountered the group of 1050 private patients with apical systolic murmurs (1000 primarily at the apex and 50 transmitted from the base), there were 1167 patients with cardiac symptoms or signs but no apical systolic murmurs at all. Of this number, 562 (or 48 per cent) had organic heart disease (including angina pectoris), 537 (or 46 per cent) appeared to have normal hearts and 68 were doubtful. Of the 562 with organic heart disease, 70 showed mitral diastolic murmurs without mitral systolic murmurs, and 71 showed important basal murmurs, leaving 421 cases with abnormal hearts but no murmurs at all—a percentage of 31 of my entire series of 1359 cases of organic heart disease in this group of 2217 patients analyzed. This large number of cases of organic heart disease without murmurs shows the great need of careful examination by percussion, palpation, blood pressure studies, and at times Roentgen ray and electrocardiography, as well as by auscultation. This group is incidentally a very important one prognostically as shown by the fact that

within a very few years, at least 98 (or 17 per cent) of the group of 562 organic cardiac patients without apical systolic murmurs have died, and even more interesting, 86 (or 20 per cent) of the 421 organic cardiac cases with no murmurs at all are known to be dead.

Apical Diastolic Murmurs not Transmitted from the Base. The *mitral diastolic murmur* is much simpler to assess but often difficult to hear. It is very important and should be sought for in every case. It may be heard only at a very limited area at the apex, with the bell chest piece and with the patient recumbent. It is often accompanied by a loud third heart sound. Exercise accentuates it. When it is present, it means either organic mitral stenosis, almost invariably rheumatic in origin and of varying degree and prognosis, or much less often and likely, functional or relative mitral stenosis due to dilatation of the left ventricular cavity in chronic adhesive pericarditis, aortic regurgitation, or cardiac failure. In the case of aortic regurgitation this relative mitral stenotic murmur is called the Austin Flint murmur.

Of 250 private patients of mine who showed the mitral diastolic murmur, 220 (or 88 per cent) appeared to have organic mitral stenosis. In 16 others (6.4 per cent) the mitral middiastolic murmur was associated with aortic regurgitation, in 3 cases with adherent pericardium, and in 4 others with cardiac dilatation due to other cause. In 7 cases it was not known whether organic mitral stenosis was present or not. In any case the mitral diastolic murmur is a serious sign, whether indicating organic or functional mitral stenosis, although it is occasionally compatible with a long fairly active life. Of the total 250 cases of the present series 34 (or 14 per cent) are known to have died within a very few years.

Summary and Conclusions. An analysis of 1050 unselected private patients with apical systolic murmurs, seeking medical advice because of cardiac symptoms or signs, has shown that organic heart disease was present in 797, or 76 per cent. Of this number in 50 cases the murmur was transmitted from the base. Sixty-three cases were doubtful and in only 190 (or 18 per cent) was the heart apparently not the site of structural disease. The louder the murmur the greater is the probability of organic heart disease and the worse the prognosis. Valvular disease, cardiac dilatation, or both, appear to responsible for the bulk of apical systolic murmurs in this group.

An analysis of 250 consecutive private patients with mitral diastolic murmurs has shown that true mitral stenosis is probably present in about 90 per cent, the balance being due to left ventricular dilatation associated with aortic regurgitation (Austin Flint murmur) or other conditions. Transmission of aortic diastolic murmurs to the apex occurs in about 37 per cent of the cases showing such murmurs.

Organic heart disease (including angina pectoris) is frequently found with no apical systolic or diastolic murmurs, as shown by

492 (or 36 per cent) of the present series of 1359 cases of organic heart disease, and also quite often with no heart murmurs at all, as shown by 421 (or 31 per cent) of these same 1359 cases. The organic cases without heart murmurs are as important prognostically as those with murmurs.

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WHOOPING COUGH.

Report of 20 Cases Treated with Ephedrin Hydrochlorid.

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In presenting the following clinical observation on the use of ephedrin hydrochlorid, it is not our desire to merely add one more drug to the unending list of those already advised in the treatment of whooping cough, but rather to call the attention of other observers to the possible symptomatic relief that may be obtained in a certain number of cases. We would like to stimulate further observation of a more scientific nature on cases under constant control conditions.

After reviewing the more recent literature[1] on the physiologic action of ephedrin, and having ourselves observed a series of 5 cases of asthma in children in which marked relief was obtained, we concluded that possibly the drug would give some symptomatic relief in whooping cough. With this idea in view, we have studied 20 cases of whooping cough in which we used ephedrin hydrochlorid by oral administration. Five of these cases occurred in an orphanage, where they were under fairly constant observation; the remaining 15 cases were in private homes, and in these cases we had to depend largely on the observation of the mother as to variation in symptoms.

Diagnosis. The diagnosis of whooping cough was made on the following points: (1) Definite exposure to the disease. (2) A gradually increasing cough, occurring more frequently at night, of

at least two weeks duration and spasmodic in character. (3) Absence of any considerable degree of fever and absence of any marked bronchitic condition. (4) A lymphatic leukocytosis in the majority of cases. (5) A definite whoop and vomiting following the cough. (6) Cyanosis. No attempt was made to take cultures or to make observations on the agglutination reactions.

Treatment. Vaccine treatment had been instituted in 8 cases prior to the use of ephedrin hydrochlorid.

In Cases 4, 9, 10 and 11 vaccine had been given three to five weeks previous to administration of ephedrin, due to direct exposure to whooping cough. None of these cases showed any effect from the vaccine, all developing severe cases. The doses in these cases were—(1) 1000 million, (2) 2000 million, (3) 4000 million, (4) 4000 million, fresh straight pertussis vaccine, given one day apart.

Cases 2 and 17 were given four doses of vaccine two weeks previous to the use of ephedrin hydrochlorid with no appreciable results. Dosage and type of vaccine could not be determined. Both developed severe whooping cough.

Cases 1 and 5 were given four doses of fresh straight pertussis vaccine, one and two days apart during the first week of the disease, with slight improvement but cough and vomiting were severe and increasing at time of beginning treatment with ephedrin.

Cases 1, 2, 6, 7 and 17 received ether in olive oil per rectum. There was slight improvement in 1 and 17, but no results in 2, 6 and 7. The remaining cases received neither vaccine nor ether in oil.

Dosage. Ephedrin hydrochlorid was given by mouth in a watery solution. One-quarter grain was given to children over one year of age, and $\frac{1}{8}$ grain to those younger. In 6 cases, medication was given at bedtime only, the remaining cases received ephedrin night and morning and occasionally three times a day. No other medication was used during administration of ephedrin.

The effect observed on certain symptoms is recorded on chart.

Special Features and Toxic Symptoms. 1. Marked restlessness was observed in 2 cases. These were infants five and six months of age respectively, receiving $\frac{1}{8}$ of a grain night and morning.

2. Marked abdominal distention occurred in 3 cases. This was relieved immediately in all cases when medication was discontinued, but recurred when treatment was resumed. This was due presumably, to relaxation of intestinal musculature.

3. Apparent suppression of urine for twelve hours was observed in 1 case on the fifth day of treatment, due possibly to a vasoconstriction in the kidneys as described by Chen and Schmidt.[3] Relief was obtained on discontinuing medication, but recurred on resumption of treatment. It was not possible to determine if there was later a diuresis. Examination of the urine was negative.

4. Abdominal pain and discomfort was complained of in 3 cases, occurring thirty to forty-five minutes after receiving medication.

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
				Condition before Use of Ephedrin Hydrochlorid.																
Cough	xxx	xxxx	xxxx	xxx	xxxx	xxxx	xxxx	xxx	xx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
Whoop	x	xxxx	xxxx	xx	xx	xx	xx	x	x	xxx	xxx	xxx	xxx	xxxx	xxx	xxx	xxxx	xxx	xxxx	xx
Vomiting	—	xxxx	xxxx	x	x	xxxx	xxxx	x	x	xxxx	xxxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxxx.	xxxx
Cyanosis	xx	xxx	xxxx	x	x	xxx	x	x	x	xxx	xxx	xx	xx	xxx	xx	xx	xxxx	xxx	xxx	xxx
				Condition during Administration of Ephedrin.																
Cough	xx	x	xx	x	x	x	x	x	x	x	x	x	x	xxxx	x	x	xx	x	xx	x
Whoop	—	—	xx	—	—	—	—	—	—	—	—	—	—	xxxx	—	—	—	—	—	—
Vomiting	—	—	x	—	—	—	x	—	—	—	—	—	—	xxx	—	—	—	—	—	—
Cyanosis	x	—	x	—	—	—	—	—	—	—	—	—	—	xx	—	—	—	—	—	—

xxxx indicated symptoms very marked; xxx, severe; xx, mild; x, slight; —, negative.

5. Marked sweating occurred in 2 cases. These cases also showed stupor, lasting six to eight hours. Whether this was an effect of the drug or merely due to relief of previous symptoms, we are unable to say.

6. Marked nasal discharge was noted in one case.

7. Nosebleed was relieved in one case.

8. Subconjunctival hemorrhage, gradually increasing in extent in one case, did not increase after the use of ephedrin.

Case Reports. The following brief outlines are typical of the cases observed in our series:

CASE II.—W. D. M., a white male infant, aged one year, was first seen in the latter part of the third week of whooping cough. At that time, he had a severe capillary bronchitis with a temperature of 103° F. This cleared up in about three days under treatment; but the whooping and vomiting was very severe and marked cyanosis was present. This child was given $\frac{1}{8}$ of a grain of ephedrin hydrochlorid night and morning, beginning April 7, 1927. The first night the child was restless. Cough was more frequent but there was no vomiting, cyanosis, or whooping. The following day the child coughed very little, there was no whooping, and no vomiting, but child was drowsy and sweated a great deal. On April 10, 1927, cough and all signs of whooping cough had disappeared. Treatment was continued until April 13, 1927, when it was discontinued without return of symptoms.

CASE III.—Baby R., a white male infant, aged six months, was first seen April 9, 1927, with severe whooping cough of four weeks duration. The child was having violent attacks, marked cyanosis, and mild convulsions. Ephedrin hydrochlorid, $\frac{1}{8}$ of a grain, was begun April 9, 1927, given night and morning. The next day cough was frequent but there was no whooping, cyanosis, or vomiting. The child was very restless and there was marked discharge from nose. By April 12, 1927 cough was much less frequent. There was an occasional whoop, slight cyanosis, and vomiting. Ephedrin was discontinued for eighteen hours with a marked return of whooping and vomiting. On April 15, 1927, there was very little cough, an occasional whoop, but no vomiting and no cyanosis.

CASE V.—W. L., a white male infant, aged three years, was seen at the end of the second week of whooping cough. At this time, child had moderately severe symptoms with a marked hoarseness and stridor present. Ephedrin was given, $\frac{1}{4}$ of a grain, night and morning, beginning April 8, 1927. The following day cough was much improved, hoarseness was gone, and there was no whooping or vomiting. Ephedrin was discontinued for eighteen hours with marked increase in symptoms. Ephedrin was begun again and by April 14, 1927, the only symptoms child had were those of a mild bronchitic cough.

CASE X.—L. T., a white female child, aged eight years, was first seen March 10, 1927, in the third week of a severe attack of whooping cough. This child had previously been subject to repeated attacks of asthmatic bronchitis, but showed no signs of that condition when seen at this time. She was vomiting practically all food given, and attacks of coughing were very violent. Ephedrin hydrochlorid, $\frac{1}{4}$ of a grain, was given night and morning. The following day vomiting had stopped, there was very little cough, and no whooping. Improvement continued until May 14, 1927, when the child complained of abdominal pain thirty to forty-five minutes after medication, and had marked abdominal distention. Treatment was discontinued on account of the repetition of these symptoms, with the result that whooping, vomiting, and cough became much worse and persisted.

CASE XII.—F. S., a white male child, aged five and a half years, was first seen March 7, 1927, because of alarming nosebleed. For two weeks he had suffered with a severe spasmodic cough followed by vomiting and nosebleeds. There was a history of exposure to whooping cough. The blood findings were as follows: White count, 9200; polymorphonuclears, 48 per cent; lymphocytes, 48 per cent; mononuclears, 1 per cent, and eosinophils, 3 per cent. Ephedrin hydrochlorid, $\frac{1}{4}$ of a grain, was given at bedtime, following which the nurse said that he slept better than he had in a week. The child had no further nosebleeds or vomiting, although he still had a slight cough. March 10, 1927, there were no complaints other than an occasional cough and the ephedrin was discontinued with recurrence of the paroxysmal cough and vomiting. March 12, 1927, the drug was started and given until March 21, 1927 with relief of all symptoms except an occasional cough, which lasted for about a week after discontinuing medication.

CASE XVI.—A white boy, aged four and a half years, following exposure to whooping cough, developed the disease six weeks ago and for the past four weeks has had a moderately severe cough followed by vomiting, which is worse at night. March 7, 1927, the white blood count was 21,450; polymorphonuclears, 70 per cent; lymphocytes, 27 per cent; mononuclears, 1 per cent; transitionals, 2 per cent; on this date ephedrin hydrochlorid was given in quarter-grain doses at bedtime. Two days later, his coughing spells were only of short duration, and not as severe as formerly. There had been no vomiting. March 10, 1927, the symptoms were so mild that medication was discontinued. There was a recurrence of all the former symptoms, so on March 12, 1927, the drug was again started with relief of symptoms. Ephedrin was again discontinued March 19, 1927, with no recurrence of the spasmodic cough although a slight cough persisted for two weeks.

CASE XVII.—J. T., a white female infant, aged three years, was seen in the fourth week of an extremely severe attack of whoop-

ing cough, April 11, 1927. At that time, she was having paroxysms every thirty minutes, day and night. Ephedrin hydrochlorid, ¼ of a grain, was given night and morning. The following day cough was much improved, there was no cyanosis, no vomiting, and only slight whoop. April 13, 1927, child had marked stupor and marked abdominal distention, lasting about twelve hours. Cough and vomiting were absent, there was no cyanosis. By April 16, 1927, there remained only a slight cough, with no vomiting, cyanosis, or whooping.

CASE XX.—R. T., April 13, 1927, a colored girl, aged four years, two weeks ago developed a cough that is worse at night and accompanied by a whoop. For three days she has vomited everything she eats. Last night she vomited three times following coughing attacks, and has vomited twice this morning before nine o'clock. Three days ago she developed a conjunctival hemorrhage of left eye that is gradually growing larger. Ephedrin hydrochlorid, ¼ of a grain, at bedtime was ordered. The child was not seen again until March 19, 1927, when the mother said that the child has had only an occasional cough and no vomiting since taking the medicine, so she did not report as instructed. The hemorrhage of the eye did not enlarge and is now absorbing.

Effect on Blood Pressure. Being unable to obtain blood-pressure readings under control conditions on the cases of whooping cough, nine well children were put to bed. Four control blood-pressure readings were taken the first day. The next day, after taking a reading at 8.00 A.M., ephedrin hydrochlorid, grains ¼ in 1 dram of water, was given. Readings were taken every fifteen minutes during the first hour, then every half hour during the next two and a half hours. Readings were again taken at the end of four and a half, five and a half, seven and a half, nine and a half, and twenty-four hours.

None of these cases showed a marked rise in blood pressure. Three cases had no rise. Slight rises were noted on the other six. The greatest rise was seen in the youngest of the cases, a rise of 12 mm. above the high control in thirty minutes, gradually returning to normal at the end of five and a half hours.

Three cases had marked sweating, this being the only finding noticed other than the slight elevation of blood pressure. None of these patients complained of any subjective symptoms.

Remarks. Ephedrin hydrochlorid gave relief from spasmodic cough and vomiting in 18 of 20 cases of whooping cough in which it was used. The relief in these cases may be due entirely to the relief of laryngospasm through inhibition of a pathological conditional reflex or through direct action on the sympathetic.[4] In all cases, in which improvement was noted, some cough remained but was mild and of a type associated with acute upper-respiratory infection, none of the characteristic signs of whooping cough remaining. No serious toxic symptoms were noted. No complications occurred in

these cases. It is our impression that the drug is most useful during the second stage. We also feel that smaller doses would give relief without toxic symptoms developing. Six of nine well children, whose blood pressure was followed after administration of ephedrin, showed a slight rise.

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THE CLINICAL SIGNIFICANCE OF THE CHLORID METABOLISM IN LOBAR PNEUMONIA.*

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A low chlorid excretion is one of the most constant findings in lobar pneumonia. The acute onset, the lobar distribution of the consolidated area, the termination by crisis, and the characteristic chlorid metabolism are features which typically differentiate lobar pneumonia from other acute conditions of the lung in which consolidation occurs.

Peabody[1] and others have shown that the low excretion of chlorid is due to a low level in the blood. No satisfactory explanation for this finding has been given. The exudate in the lung contains only a small portion of the chlorids retained. Analysis of other body tissues has not revealed any significant increase in chlorid content. It is the opinion of most workers that the retained chlorid must be generally distributed over the body. The blood in lobar pneumonia frequently shows also a high nonprotein content especially in the undetermined portion. This increase is probably due to accelerated protein catabolism rather than renal retention since the excretion of nonprotein nitrogen in the urine is high. Studies on the CO_2 combining power[2,3,4,5] show that an acidosis of metabolic origin is a rarity in lobar pneumonia. There is often a true alkalosis.

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Certain other widely different clinical conditions show strikingly similar chemical findings in blood and urine. In experimental pyloric and intestinal obstruction[6,7] the chlorids disappear rapidly from the blood, usually with a coincident alkalosis. These changes seemingly precede the tissue destruction and increased nonprotein nitrogen content of the blood. The toxemia which is a most characteristic feature of the disease is seldom evident until the chlorids have fallen below a certain level. It has also been shown that keeping the blood chlorids near the normal prevents the toxemia. Dogs with the jejunum obstructed have been kept alive as long as thirty-one days without developing a toxemia; while untreated dogs die on an average in four days.[8,9] Likewise, supplying the needed chlorids, after the blood chlorids have reached a low level and the toxemia is already under way, has usually influenced most favorably the course of the toxemia. The results obtained in clinical work have paralleled the experimental results in dogs.[10]

The fact that the toxemia of intestinal obstruction does not develop in untreated animals until the chlorid reserve is well depleted and can be prevented by providing an ample supply of chlorids, suggests that the utilization of chlorids here is a protective mechanism on the part of the body.

In Roentgen ray intoxication Cameron and McMillan[11] have found a marked lowering of chlorid excretion with a high nitrogen excretion. Sodium chlorid will prevent or lessen the sickness. They think that the chlorid acts in a detoxicating manner.

Davidson[12] has demonstrated a striking alteration in chlorid metabolism in cutaneous burns. The blood chlorids are low and the chlorid excretion is diminished proportionate to the amount of tissue devitalized. The protein catabolism is much increased. Davidson states that the clinical condition of patients with severe burns is well reflected in the level of the blood chlorids. He suggests the use of sodium chlorid as a therapeutic agent. Bigger[13] has independently treated a group of cases with sodium chlorid with excellent results.

In serum disease Longcope, Rackemann and Peters[14] found a marked diminution in chlorid excretion during the acute symptoms of the disease. The blood chlorids were below the renal threshold.

Seemingly the common factor in the widely different clinical conditions showing such strikingly similar chemical findings is a protein intoxication usually of unknown origin. The exact toxic agent is also unknown. In all these conditions there is an accelerated protein catabolism with high nitrogen and low chlorid excretion and a low chlorid and high nonprotein nitrogen in the blood. There is often an alkalosis. An acidosis seldom occurs.

The striking results obtained with sodium chlorid in both preventing and combatting the toxemia of pyloric and intestinal obstruction

affords a rational basis for its use in lobar pneumonia. Numerous articles were published 20 to 25 years ago on the saline treatment of lobar pneumonia. The first clinical report is that of Penrose in 1899.[15] Solis-Cohen[16] gives the credit for its introduction to F. P. Henry of Philadelphia who, he states, used it as early as 1890.

Most clinicians employed saline infusions as a means of producing increased excretion of toxins through the kidneys. Others definitely used sodium chlorid as a detoxifying agent. Sajous[17] thought that the early use of saline solution would produce the effects one wished to get with immune sera. Wakefield[18] pointed out that chlorid is a sort of prototype of oxygen and can enter into combination in place of oxygen in conditions of suboxidation. This observer thought that antitoxins in pneumonia are produced by oxidation. The utilization of chlorid according to this view is a protective measure on the part of the body in an attempt to hasten the formation of antibodies. Peabody,[1] in studying the blood chlorids in pneumonia, gave small amounts of sodium chlorid to note the effect on the blood chlorids. Prigge[19] has reported 11 cases of pneumonia in which a single intravenous injection of 20 to 38 gm. of sodium chlorid was given. He states that all of the chlorid was excreted within four days after it was given and that the chlorid metabolism in pneumonia patients differed from normal controls only in the greater length of time required to excrete the chlorid injected.

We have observed a small group of patients with lobar pneumonia from the standpoint of blood and urine chemistry. Metabolic studies have been made on several patients treated with sodium chlorid.

Clinical Observations. The typical findings on chemical analysis of the blood and urine in lobar pneumonia are shown in Table I. In each instance only a trace of chlorids was found in the urine. Often the excretion is much less than one would expect from the level of the blood chlorid although this was always below normal. The nonprotein nitrogen and urea nitrogen were high in three, normal in one and only slightly elevated in one.

In Table II are shown the findings in a patient treated with sodium chlorid. This patient developed a typical lobar pneumonia after an appendectomy. He was given 74 gm. of sodium chlorid by mouth the first four days of his illness. During this period the total excretion was 7.23 gm. The blood chlorid remained well below the normal level during this time.

Patient B (Table III) was very ill on admission to the hospital. The pulse was 128, respiration 42 and blood pressure low. Large amounts of salt were given by mouth. His condition remained satisfactory throughout the course of the disease. He developed empyema but finally recovered completely. This patient was given 160 gm. of salt by mouth in addition to that taken with food. During this period only 93.4 gm. were excreted. The fall in urea nitrogen and nonprotein nitrogen after the administration of the sodium chlorid was begun is very striking.

TABLE I.—TYPICAL BLOOD CHEMICAL FINDINGS IN LOBAR PNEUMONIA.

Patient.	Day of disease.	Blood. Mg. per 100 cc. Total non-protein nitrogen, mg.	Urea nitrogen, mg.	Chlorids, mg.	CO_2 combining power, vol. per cent.	Urine chlorids, per cent.
1	3	65.5	32.3	380	43.8	0.08
	4	72.8	32.2	400	44.7	Trace
	5	78.0	41.1	400	45.7	
	6	82.5	40.6	410	55.1	
	8	57.8	26.2	390	47.5	0.23
	10	45.6	21.0	400	49.4	0.40
	12	30.3	13.1	420	49.4	0.70
2	3	30.0	14.0	360	47.5	0.10
	4	...	15.8	350	46.6	
	6	...	14.0	370	49.4	
	8	29.4	12.1	360	49.4	
3	11	41.6	19.6	390	53.2	0.06
	12	41.6	17.8	350	52.2	0.07
	14	34.9	18.2	410	55.1	
	16	30.0	16.4	410	49.4	0.80
4	5	33.3	9.34	430	32.8	0.15
	6	52.6	26.2	440	45.7	0.10
5	7	98.4	50.0	390	36.2	

TABLE II.—CHEMICAL FINDINGS IN BLOOD AND URINE OF PATIENT WITH LOBAR PNEUMONIA TREATED WITH SODIUM CHLORID.

Patient A. Date.	Blood. Chlorids, per 100 cc., mg.	CO_2 combining power, vol. per cent.	Urine chlorids. Per cent.	Total, gm.	Sodium chlorid given, gm.
Dec. 21	....	....	0.04	1.44	10
22	370	....	0.07	1.54	16
23	390	....	1.04	1.77	24
24	....	....	0.08	2.48	24
25	370	51.3	0.15	9.30	0
26	400	....	1.13	6.89	0
27	380	....	0.10	1.50	0
28	....	....	0.30	7.50	0
29	480	55.1	0.40	5.60	0
30	480	....	0.40	5.60	6
31	380	....	0.41	4.10	6
Jan. 1	400	46.6	0.60	5.04	6
2	....	....	0.74	6.60	6
3	....	....	0.87	5.22	6
4	....	....	0.80	6.00	6
5	....	....	0.73	1.18	6
6	....	....	1.18	3.78	6
7	....	....	1.23	8.00	6
8	....	....	1.00	11.50	6
9	....	....	1.12	6.77	6
10	....	....	1.00	7.00	6
11	....	....	1.00	7.00	6
Total	....	....	....	112.61	152

TABLE III.—CHEMICAL FINDINGS IN BLOOD AND URINE OF PATIENT WITH LOBAR PNEUMONIA TREATED WITH SODIUM CHLORID.

Patient B. Day of disease.	Nonprotein nitrogen, mg.	Blood. Mg. per 100 cc. Urea nitrogen, mg.	Blood. Mg. per 100 cc. Chlorids, mg.	CO_2 combining power.	Urine chlorids. Per cent.	Urine chlorids. Grams.	Sodium chlorid given, gm.
3	45.6	20.3	390	65.5	Trace	...	8
4	43.6	28.7	450	55.0	0.07	0.42	36
5	28.2	10.5	480	50.0	0.53	6.90	16
6	28.9	9.8	450	43.8	0.63	15.70	12
7	19.4	10.5	500	45.7	0.24	3.80	0
8	...	...	...	...	0.15	1.50	7
9	...	...	...	...	0.13	1.60	16
10	25.4	11.2	470	41.9	0.30	4.60	16
11	...	...	...	...	0.70	11.20	14
12	...	...	...	...	0.92	16.10	17
13	...	...	...	...	0.93	18.10	14
14	...	...	...	...	0.50	8.30	4
15	...	...	...	...	0.22	9.20	
Total	...	...	...	...	...	93.40	160

TABLE IV.—CHEMICAL FINDINGS IN BLOOD AND URINE OF PATIENT WITH LOBAR PNEUMONIA TREATED WITH SODIUM CHLORID.

Patient G. Date.	Blood. Mg. per 100 cc. Nonprotein nitrogen, mg.	Blood. Mg. per 100 cc. Urea nitrogen, mg.	Blood. Mg. per 100 cc. Chlorids, mg.	CO_2 combining power.	Urine. Chlorids, per cent.	Urine. Nonprotein nitrogen, per cent.
Mar. 6	116.0	58.1	370	47.5	0.04	
7	...	30.8	360	38.1		
8	...	44.2	350	...	0.06	
9	81.5	32.9	360	48.5	0.08	1.00
10	76.5	25.8	340	52.0	0.13	1.65
11	50.5	27.2	430	47.5	0.12	1.77
12	34.5	21.0	440	50.2	0.16	1.50
13	...	18.9	440	50.2	0.29	2.30
14	32.6	20.3	350	47.5	...	1.04
16	...	...	...	...	0.38	1.59
17	...	...	...	...	0.51	

Patient G (Table IV) presented the typical picture of lobar pneumonia. On admission, the right lower lobe was consolidated. Later the entire right side was involved. The nonprotein nitrogen on admission was 116 mg. per 100 cc. This patient was given 1 gm.

of salt by mouth every hour. He developed a septic arthritis of the knee, a thrombophlebitis and subcutaneous abscesses indicating the serious type of infection, but made a satisfactory recovery. This patient had a very high nonprotein-nitrogen excretion in the urine.

A number of other patients have been treated. In these complete metabolic studies could not be made, so they are not included in the tables. In every patient a beneficial effect from the treatment was evident. One patient was admitted in a very critical condition. He was given 2 per cent sodium-chlorid solution intravenously with marked improvement and final recovery. Another patient had a pneumonia migrans with consolidation finally of all lobes. He also recovered.

The patients under treatment with sodium chlorid remain in a very satisfactory condition considering the severity of the infection. The cyanosis is not marked, the blood pressure remains up, the abdomen is soft and the pulse good. In upper gastro-intestinal tract obstruction there is seemingly some relation between the oxygen saturation of the blood and the salt content. This relation probably holds true in pneumonia also.

Usually the salt was given in uncoated tablets by mouth. In extreme cases it should be given intravenously as a 1 or 2 per cent solution preferably dissolved in 10 per cent glucose solution. When given by mouth 1 or 2 gr. should be given every hour until the sodium-chlorid concentration of the urine is normal.

Summary and Conclusions. In lobar pneumonia the blood shows almost constantly a low chlorid content. Often the urea nitrogen and nonprotein nitrogen are high. The CO_2 combining power is seldom below normal.

The urine shows very little chlorid and usually a high nitrogen content.

The use of sodium chlorid in the small series here reported seemingly had a marked therapeutic effect in patients suffering from lobar pneumonia.

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PREËXISTING SYPHILIS AS CAUSE OF UNRESOLVED PNEUMONIA AND A FACTOR IN THE PRODUCTION OF CERTAIN OTHER POSTPNEUMONIC COMPLICATIONS.

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The failure of resolution in pneumonia is an untoward event of sufficient frequency and importance to warrant the most serious efforts for its prevention. In itself it is an important complication, leading to the development of chronic fibroid pneumonia. In addition, it is probably associated, in some cases at least, with the development of more serious complications, such as lung abscess, gangrene, bronchiectasis, etc. Unfortunately, the mechanism of resolution and, therefore, the factors concerned with failure of resolution are but imperfectly understood. It is even more important, then, that any known condition or circumstance influencing this phenomenon should be thoroughly studied and its importance and frequency determined.

Strangely enough, the possible influence of preëxisting syphilis on the resolution of pneumonia has been neglected. The literature contains but scanty reference to it and, in particular, textbooks and works of reference are silent concerning this important possibility. Among the few studies of the influence of syphilis on the resolution of pneumonia are those by Head and Seabloom,[1] in 1919, Fitz-Hugh,[2] in 1924, and Fitz-Hugh and Anderson,[3] in 1926. Brief reference to it was made by Piersol,[4] in 1921, and Simonton, in the discussion of the paper by Piersol, described briefly 3 such cases. Fitz-Hugh has given credit to Head and Seabloom for first calling attention to the influence of syphilis in this connection. The possible importance of syphilis as a factor in the nonresolution of pneumonia becomes greater when one realizes that as such it is susceptible of control from the diagnostic, prophylactic and curative points of view.

The attention of one of us (J. B. Y.) was first called to the possible importance of syphilis in this regard some years ago. The recent observation of several cases of postpneumonic complications occurring in syphilitic patients served to again direct our attention to this subject, and suggested that syphilis may play a part, not only in the occurrence of simple delayed resolution and nonresolution, but also in the development of more serious complications, such as lung abscess and bronchiectasis. Such an important possibility seemed to us to warrant a more thorough study. We have, therefore, reviewed a series of cases of postpneumonic complications occurring in the University Hospital, and such a study constitutes the basis of this paper.

For the purpose of this study we have selected all the cases of unresolved pneumonia and postpneumonia lung abscess, bronchiectasis and chronic fibroid pneumonia occurring during the period of five and a half years, from July, 1921, to January, 1927. These cases are divided into two groups: (1) Those in living persons in whom the diagnosis is based on the facts disclosed by the history and physical examination, including roentgenologic findings; (2) those cases discovered or confirmed by necropsy. The comparative rarity of acute pneumonia in this hospital has prevented any worthwhile study of the frequency with which syphilis influences the course of this disease in general.

TABLE I.—GROUP I. CASES IN LIVING PERSONS.

Case No.	Age.	Sex.	Postpneumonic lesion.	Duration.	Wassermann.	History of syphilis.
I	28	M.	Lung abscess	7 mos.	−	Primary lesion.
II	46	M.	Unresolved pneumonia, bronchiectasis	3 yrs.	−	
III	34	M.	Unresolved pneumonia, bronchiectasis	5 mos.	−	
IV	35	M.	Unresolved pneumonia, bronchiectasis	4 yrs.	++++	
V	17	F.	Unresolved pneumonia, bronchiectasis	11 mos.	− ++*	Exposure.
VI	39	M.	Bronchiectasis, abscess	3 "	1+†	Antisyphilitic treatment years before.
VII	38	F.	Nonresolution	3–4 wks.	++++ †	
VIII	34	M.	Unresolved pneumonia, abscess	3½ mos.	++++	Primary lesion five years before.
IX	57	M.	Abscess	9 "	++++	Primary lesion; Wassermann 4+, five years ago; treated.
X	54	F.	Bronchiectasis, abscess	20 yrs.	++++ −	Antisyphilitic treatment.

* Kahn. † Twice.

In the period of five and a half years there have occurred 30 cases of what we have considered to be such postpneumonic com-

TABLE II.—GROUP II. NECROPSY CASES.

Case No.	Age.	Sex.	Wassermann.	Duration of pulmonary process.	Pathologic findings.
I	43	M.	++++	5 wks.	Unresolved pneumonia with bronchiectatic abscesses; multiple pleurobronchial fistulæ; pyopneumothorax; active syphilis (leptomeningitis).
II	47	F.	++++	1 mo.	Old atelectasis; carnification; microscopically large areas of fibrosis; syphilis (mesaortitis, leptomeningitis, myocarditis, pancreatitis), purulent exudate in many bronchi.
III	55	M.	+	3 mos.	Chronic fibroid pneumonia; chronic empyema; chronic purulent bronchitis; syphilis (ruptured saccular aneurysm at bifurcation of abdominal aorta).
IV	47	M.	−	3 yrs.	Delayed resolution with diffuse organizing pneumonia, beginning carnification; syphilis (mesaortitis, myocarditis, leptomeningitis, orchitis).
V	?	M.	−	4 "	Unresolved pneumonia with bronchiectatic abscesses on right; chronic right-sided empyema; recent left empyema and croupous pneumonia with gray hepatization; latent syphilis (aortitis, orchitis).
VI	34	M.	++++	2½ mos.	Croupous pneumonia, early gray hepatization; aspiration bronchopneumonia with beginning gangrene; syphilis, caseating gummata of lung, with chronic fibroid pneumonia; primary squamous-cell carcinoma of esophagus.
VII	66	M.	−	"Several years"	Chronic purulent fibroid pneumonia; bronchiectasis with bronchiectatic abscesses; syphilis (myocarditis, orchitis); fibrinous purulent lobular pneumonia; carcinoma of bladder obstructing both ureters.
VIII	59	M.	−	3 yrs.	Nonresolving croupous pneumonia of left lower lobe, with multiple abscesses; syphilis (mesaortitis, adrenalitis); chronic purulent osteomyelitis of ribs.
IX	55	M.	++++	6 mos.	Chronic fibroid purulent pneumonia on left with multiple chronic bronchiectatic abscesses; syphilis (aortic aneurysm ruptured into main left bronchus, advanced mesaortitis, myocarditis, leptomeningitis).
X	50	M.	−	2 "	Organizing croupous pneumonia and chronic fibroid pneumonia in right midlung; multiple abscesses and areas of gangrene in lower right lung; recent aspiration lobular pneumonia, early gangrene left lung; orchitis fibrosa syphilitica; squamous carcinoma of esophagus, with tracheoesophageal fistula.
XI	8*	M.	−	...	Acute purulent bronchopneumonia; old unresolved croupous pneumonia with abscess; septicopyemia.
XII	46	F.	?	13 mos.	Chronic fibroid pneumonia with bronchiectasis; acute purulent bronchopneumonia; softening left caudate nucleus.
XIII	49	M.	−	?	Delayed resolution of croupous pneumonia; pernicious anemia; multiple degeneration of spinal cord; advanced atherosclerosis.
XIV	17	M.	−	3 yrs.	Chronic fibroid pneumonia (left) with bronchiectasis; brain abscess; tuberculous bronchial nodes.
XV	42	M.	−	10 mos.	Chronic fibroid pneumonia with bronchiectasis; chronic empyema; unresolved pneumonia lower right lung; purulent bronchopneumonia.
XVI	67	F.	−	2 "	Nonresolving right-sided croupous pneumonia with multiple abscesses and gangrene.
XVII	60	F.	No record	2 wks.	Organizing unresolved croupous pneumonia; acute bronchopneumonia; pleuritis with empyema; mitral stenosis.
XVIII	43	M.	NoWass.	2 "	Chronic organizing purulent pleuritis on left, with organizing unresolved croupous pneumonia; purulent bronchitis; acute fibrinous pericarditis.
XIX	57	F.	−	1 yr.	Unresolved croupous pneumonia; chronic fibroid pneumonia with carnification on right; right empyema; recent fibrinopurulent bronchopneumonia with multiple abscesses and infected infarcts.
XX	55	M.	−	?	Unresolved croupous pneumonia with areas early organized; multiple abscesses; diffuse chronic purulent bronchitis with bronchiectatic abscesses.

* Months.

plications. Of this number 10 were in living persons and constitute the cases in Group I. Twenty cases were discovered or confirmed at necropsy and constitute Group II. In Tables I and II are given in summarized form the data regarding these two groups of cases.

Of the 10 patients in Group I 1 had an unresolved pneumonia, 5 unresolved pneumonia and lung abscess or bronchiectasis and 4 had lung abscess, bronchiectasis, or both. Of the 20 cases in Group II 7 had an unresolved pneumonia with or without fibroid pneumonia and 13 had unresolved pneumonia with lung abscess or bronchiectasis.

Of the 10 patients in Group I 6 are considered to have had syphilis and 2 were possibly syphilitic. Of these 8 cases 4 had a strongly positive (4+) Wassermann reaction; 1 had a weakly positive (1+) reaction on two occasions and had had antisyphilitic treatment; 1 had a negative Wassermann reaction but a 2+ Kahn reaction; in 1 case the Wassermann reaction was strongly positive (4+), followed by a negative reaction after short treatment; finally, in 1 case the Wassermann reaction was negative, but the patient gave a history of a primary lesion and had received antisyphilitic treatment. In the remaining 2 cases in Group I there was no evidence of syphilis and the Wassermann reaction was negative.

Six of the 20 cases in Group II showed the presence of syphilis at necropsy, grossly and microscopically, and 4 others possibly had syphilis. Of the 6 cases showing undoubted syphilis the Wassermann reaction was strongly positive (4+) in 4, weakly positive (1+) in 1 and negative in 1. Of the 4 cases possibly syphilitic the Wassermann was negative in all. Of the 10 cases showing no evidence of syphilis the Wassermann reaction was negative in 7 and not reported in 3. Brief abstracts of the cases considered to have proven syphilis in both Groups I and II are given below:

Abstracts of Cases. *Group I.* CASE I.—S. W., a white male, aged twenty-eight years, had pneumonia eight months before admission; this was followed by empyema which drained seven months. Since the onset the patient has raised a cupful of purulent, often blood-streaked sputum daily. There has been a loss of 20 pounds. He was treated for acute gonorrheal and syphilitic infection six years before. Examination revealed retraction of the right chest accompanied by immobility, dullness at the right base with bronchial breathing and egophony. The sputum was negative for tubercle bacilli. The Wassermann was negative. The Roentgen ray examination indicated lung abscess with inflammatory process. Diagnosis: Lung abscess.

CASE IV.—N. M., a white male, aged thirty-five years, four years ago, immediately after an appendectomy, developed a typical pneumonia. Since then there has been cough and a loss of 30 pounds in weight. He had a gonorrheal infection at nineteen years. Examination showed dullness at the right base. The Wassermann was 4+. Roentgen ray showed thickened pleura at the right base, with marked diffuse fibrosis of the lower lung, and bronchiectasis. Diagnosis: Unresolved pneumonia with bronchiectasis.

CASE VI.—R. H., a white male, aged thirty-nine years, three years ago, was confined to bed for one month with pneumonia and pleurisy. Since then there had been persistent cough, accompanied by much thick, green sputum, a total of three cupfuls per day. There had been a loss of 70

pounds. The patient was in three different sanatoria, without a diagnosis of tuberculosis ever being made. Examination showed a lag of the right chest on inspiration. Dullness was found at the right apex and base, and amphoric breathing and moist râles were heard in the right axilla. Several thoracenteses failed to locate any fluid. Repeated sputum examinations were negative for tubercle bacilli. The Wassermann reaction was 1+; a similar reaction was obtained some years before while the patient was under antisyphilitic treatment at this hospital. Roentgen ray revealed a dense shadow which occupied the lower right lung field; also thickened pleura. Diagnosis: Unresolved pneumonia with probable bronchiectasis and abscess.

CASE VII.—L. M., a white female, aged thirty-eight years, had a pneumonia four weeks before, since which time there had been intermittent fever, cough and purulent sputum. Examination showed limited expansion at the left base. At the right base dullness extended down from the midscapular region, in the right axilla and right front. Breath sounds were bronchovesicular. Bronchophony, pectoriloquy and coarse râles were heard over these areas. The leukocyte count was 40,000. The Wassermann was reported 4+ on two occasions. The Roentgen ray showed nonresolution. Diagnosis: Unresolved pneumonia.

CASE VIII.—T. F., a white male, aged thirty-four years, three and a half months before admission, had symptoms of pneumonia, onset with chill, fever, cough and sputum, but did not go to bed. Since then he had had chills, fever, pain in the right chest, persistent cough and a fairly large quantity of foul, purulent, often blood-streaked sputum. These symptoms forced him to quit work; there had been a loss of 18 pounds. Examination revealed lag of the left chest on inspiration. There was flatness at the left base, from the angle of the scapula down, and extending anteriorly to the midaxillary line. Breath sounds were amphoric at the angle of the scapula. Elsewhere this area showed bronchial breathing and bronchophony. There was a history of a primary genital lesion five years before. Sputum was negative for tubercle bacilli. The Wassermann was 4+ on two occasions. Roentgen ray indicated an unresolved pneumonia of the left lower lobe, on first examination. Two months later "the left lung showed irregular infiltration—abscess with evidence of localized bronchiectasis." Diagnosis: Unresolved pneumonia with abscess, and probable bronchiectasis.

CASE IX.—J. S., a white male, aged fifty-seven years, had pneumonia nine months before, since which time there had been weakness, loss of 28 pounds of weight, and periods of productive cough with sputum often blood-streaked. Examination showed diminished tactile fremitus of the right lower chest, front and back, with dullness over the right base, front and back. Breath and voice sounds were diminished and a few râles were heard. Repeated sputum examinations were negative for tubercle bacilli. The leukocyte count was 15,000. The Wassermann was 4+. There was a history of chancre twenty-seven years before; five years before the Wassermann was 4+ at another clinic and a course of antisyphilitic treatment was given. Roentgen ray revealed increased density of the lower two-thirds of the right lung. A cavity with a fluid level and air above could be demonstrated. Surgical drainage was instituted. Diagnosis: Lung abscess.

Group II. Necropsy Cases. CASE I.—C. W., a white male, aged forty-three years, had pneumonia five weeks before admission. The cough continued, and three weeks before admission the patient began to raise very foul sputum; for these three weeks there had been dull pain in the

right chest, made worse on breathing. Examination revealed rapid respiration with expiratory grunt. There was a lag on the right side on inspiration. The right base, posteriorly, showed flatness, absent tactile fremitus, bronchovesicular breath sounds, moist râles and diminished voice sounds. A metallic tinkle was obtained in right midaxilla. There was hyperresonance over the upper right lung. Two liters of foul fluid were obtained by thoracentesis. The leukocyte count was 20,000. The Wassermann was 4+. Roentgen ray showed hydropneumothorax of the right chest. Necropsy revealed unresolved pneumonia with bronchiectatic abscesses; multiple pleurobronchial fistulæ, pyopneumothorax, active syphilis, namely, leptomeningitis.

Case II.—W. H., a white female, aged forty-seven years, entered the hospital in a semiconscious condition, and therefore the history was practically not obtainable. There had been a history of headache, dizzy spells and loss of consciousness. The Wassermann had been 4+ one month before, when she was treated with arsphenamin and potassium iodid. The patient was married twice, and contracted the syphilitic infection from the first husband. At examination the patient was found to be delirious. There were moist râles over both lung fields. The heart was enlarged to the left; systolic blood pressure was 300 mm. mercury. Necropsy showed old atelectasis in the posterior part of the lung; no pneumonic areas, but purulent exudate in many bronchi of both lungs; carnification; microscopically, large areas of fibrosis without trace of alveoli, of complete atelectasis with organization; syphilis (mesaortitis, leptomeningitis, myocarditis and pancreatitis).

Case III.—J. P., a white male, aged fifty-five years, had a pneumonia three months before, followed by continued fever, cough and large amounts of bloody sputum. Examination showed dullness at the right base with definite change in the breath and voice sounds. There was an aortic diastolic murmur and Corrigan pulse. The Wassermann was 1+. Necropsy showed chronic fibroid pneumonia, with chronic empyema; chronic purulent bronchitis on the right; syphilis (ruptured saccular aneurysm at the bifurcation of the abdominal aorta).

Case IV.—J. M., a white male, aged forty-seven years, was too ill to give a satisfactory history. There were three probable attacks of pneumonia within the previous three years. The clinical diagnosis was bilateral bronchopneumonia. The Wassermann was negative. Necropsy showed delayed resolution with diffuse organizing pneumonia and beginning carnification; syphilis (mesaortitis, myocarditis, leptomeningitis, orchitis).

Case VI.—G. S., a white male, aged thirty-four years. A satisfactory history was not obtained. He had complained of severe cough of four or five days' duration, following which he developed soreness in the chest. This had occurred one year before, and had persisted throughout this time. Upon examination a friction rub and râles were heard at the right base. Roentgen ray showed an inflammatory process in the right middle lobe. The patient then developed an acute pneumonia involving the right lower lobe, and Roentgen ray examination showed that the process had extended to the right lower lobe as well. There was no metastasis. Later examination showed evidence of partial resolution. Finally, the patient had several severe pulmonary hemorrhages, developed an aspiration pneumonia and died three months after admission. There was a history of primary and secondary syphilis with treatment. The Wassermann was 4+. Necropsy showed syphilis, caseating gummas of the lung with chronic fibroid pneumonia, croupous pneumonia, early gray hepatization; aspiration

bronchopneumonia with beginning gangrene; stricture of the esophagus, primary squamous-cell carcinoma.

CASE IX.—J. A., a white male, aged fifty-five years, developed a pneumonia six months before. He did not improve, there being persistent fever, cough and sputum, which forced him to quit work. Thoracotomy was done, with drainage for three weeks. The symptoms persisted; there had been loss of weight. Examination showed a tracheal tug. Expansion of the left chest was limited. Bronchovesicular breathing was heard at the left apex, front. There was dullness and absence of breath sounds below the second rib. Over the right lung were heard moist râles and bronchial breathing. The heart was enlarged to the left; there was a diastolic thrill; a blowing diastolic murmur was heard along the left border of the sternum. There was a rough systolic murmur at the aortic area. The Wassermann was 4+. Roentgen ray examination indicated a thickened pleura on the left. Necropsy showed chronic fibroid purulent pneumonia on the left, with multiple chronic bronchiectatic abscesses; chronic adhesive pleurisy, syphilis (aortic aneurysm ruptured into main left bronchus, advanced mesaortitis, myocarditis and leptomeningitis).

Discussion. The above data suggest that preëxisting syphilis plays an important role in the occurrence of postpneumonic complications, not only that of nonresolution and fibroid pneumonia, but also of pulmonary abscess and bronchiectasis which are probably in this instance closely associated with the failure of resolution. Doubt may be expressed, however, whether syphilis occurs as a factor in postpneumonic complications as frequently as our findings indicate. It is probable that the incidence obtained above represents a higher incidence than would occur in a larger series, including cases of mild postpneumonic complications. The clinical material at this hospital does not give a sufficient number of cases of acute pneumonia and the milder forms of the complications to determine the true incidence in this regard. Such considerations, however, do not seem to us to outweigh the evidence presented above, and it seems to us probable that syphilis plays a large and hitherto unappreciated role in the occurrence of these complications following pneumonia, as indicated by the frequency with which it is found in this series of severe complications. In support of this conclusion are the observations of Fitz-Hugh[2] on the incidence of delayed resolution in acute pneumonia associated with preëxisting syphilis. Though made on a small series, they are in accord with our conclusions, as are the few other reports in the literature. Although the incidence of syphilis in this connection may appear high, when one considers the relative infrequency of serious postpneumonic complications and the general incidence of syphilis, it does not appear at all improbable. The probable influence of syphilis in the cases above is indicated by comparison with a group of 16 cases of lung abscess, bronchiectasis and gangrene not postpneumonic. Of the 16 cases 13 gave a negative Wassermann reaction, in 3 the Wassermann reaction was not reported and in none was other evidence of syphilis present. It is, of course,

obvious that all syphilitics who have pneumonia do not develop such postpneumonic complications, but the exact frequency with which preëxisting syphilis influences the course of pneumonia must await the result of studies on a larger series of cases.

If syphilis is as important a cause of nonresolution and other pulmonary complications of pneumonia as our findings seem to indicate, the question at once naturally arises as to the reasons for the lack of general appreciation of so important a factor. Two possibilities, among others, immediately suggest themselves. The first is failure to heed the evidence of a positive Wassermann reaction on an assumption of nonspecificity of the reaction in the presence of an acute infectious illness, an assumption generally considered false in the light of present-day knowledge. The second, and to us much more frequent and important cause, is the failure to search for evidence of syphilis in patients with pneumonia. The course of events as we see it is somewhat as follows: The patient is seen severely ill with acute pneumonia. The diagnosis is usually obvious, the prognosis established and the patient too sick for thorough questioning. The need for a Wassermann test, balanced against a desire not to disturb the patient, is not evident. If the course is stormy, or if the patient fails to progress as is expected, the possibility of syphilis as a cause is not recognized and no particular attempt is made to discover the presence of this disease, though every effort is made to determine the possible presence of empyema, lung abscess, tuberculosis and the like. Also, our experience indicates that many of these patients apparently recover subjectively in a considerable measure from the immediate effects of the pneumonia and not for some time after is it realized that their recovery has not been complete. As a result, the patient develops insidiously a complication which may remain obscure for a considerable time, until the progress of the chronic process sends the patient in search of aid. Then it is probable, as Piersol has suggested, that with discovery of the syphilis, the condition will be diagnosed syphilis of the lung instead of what it truly is, that is, nonspecific failure of resolution of pneumonia, with or without other complications, occurring in a syphilitic individual.

The mechanism by which syphilis produces this error in resolution is not clear, nor can it be until more is learned of the process by which resolution normally occurs. As Fitz-Hugh has pointed out, several possibilities present themselves: (1) The patient may have had a preëxisting syphilis of the lung, which, lying dormant, has been aroused to activity by the pneumonia; (2) the pneumonia may have determined the site of development of syphilis of the lung in an area previously free from disease; (3) the acute lesion may have been syphilitic from the beginning; (4) the presence of a preëxisting syphilis may, by upsetting the delicate balance of physicochemical forces concerned with resolution, cause non-

specific failure of resolution with or without added pulmonary abscess, bronchiectasis and so forth.

In none of the cases reported above have we any definite information regarding the condition of the lung before the pneumonia developed. In 1 case reported by Fitz-Hugh[2] he was able to watch the development of a lesion in a part of the lung previously free and follow this lesion to the stage of nonresolution. This, together with the fact that lung syphilis, itself extremely rare, seldom exists in a form like the lesions observed in these cases, makes the first of the possibilities extremely unlikely. What is more conclusive, however, the absence, on gross and microscopic examination of the tissue, of characteristic or suggestive syphilitic lesions practically excludes the possibilities that these lesions are of themselves syphilitic. It seems much more likely that the mechanism is one of a disturbance of the various factors concerned with resolution. Analogous instances of the influence of syphilis are seen in other disease conditions and lend support to this explanation. Thus, syphilis is said to exert a similar influence in the union of fractures and in the healing of wounds, both of which may be delayed by the presence of a preëxisting syphilis. In neither of these instances is it thought that the cause is ordinarily the presence of an actual syphilitic lesion.

It is fortunate that syphilis as a factor in the nonresolution of pneumonia and the occurrence of postpneumonic complications is susceptible to control and that there is thus offered a means of preventing a certain number of such unfortunate results of this disease. To recognize this condition at the stage represented by the cases reported above is obviously of no advantage. They have then reached a point where relatively permanent damage of a type not amenable to antisyphilitic therapy has occurred; the possibility of cure is slight and even partial relief is difficult. Attention should be directed to prevention or cure at an early age. For this, several things are necessary:

1. A recognition of the possible influence of preëxisting syphilis on the course of pneumonia; further investigation of this problem should be made, and attention should be directed to this possible action of syphilis in order that continued observation may determine how important and frequent a factor it is.

2. Particular care should be used to determine the presence or absence of syphilis in patients with pneumonia and unusual efforts should be made to secure a Wassermann test instead of neglecting it because of the obvious diagnosis of pneumonia.

3. If evidence of syphilis is obtained treatment should be instituted as soon as is deemed permissible, probably before the crisis; treatment should be continued vigorously during convalescence.

4. In all cases of suspected delayed resolution or other postpneumonic complications, strict search should be made for the presence of syphilis, and if found, treatment should be begun at once.

Summary and Conclusions. 1. The records of 30 patients with postpneumonic complications (unresolved pneumonia, fibroid pneumonia, pulmonary abscess and bronchiectasis) occurring during the period of five and a half years, from July, 1921, to January, 1927, have been studied. In 10 instances the patients are living and in 20 the condition was discovered or confirmed at necropsy. Of the 10 living patients 6 showed definite evidence of syphilis and 2 were possibly syphilitic. Of the 20 necropsy cases 6 showed the presence of syphilis and 4 may have had syphilis. Thus, of the total of 30 cases of such postpneumonic complications at least 12, or 40 per cent, occurred in association with preëxisting syphilis.

2. Preëxisting syphilis is apparently an important and frequent cause of nonresolution of pneumonia and of associated postpneumonic pulmonary complications. As such its importance has been insufficiently appreciated.

3. The failure of resolution in pneumonia and the occurrence of associated pulmonary complications due to the influence of preexisting syphilis are preventable. Recognition of this fact, together with prompt and adequate treatment should make it possible to reduce the number of such complications.

4. The presence or absence of syphilis should be determined in all cases of acute pneumonia and in all cases of suspected delayed or nonresolution and postpneumonic complications.

5. Recognition of such a possible influence of syphilis should stimulate further investigation of this problem.

NOTE.—Since the paper was written an additional case has been observed, a brief abstract of which is as follows:

C. D., a white male, aged thirty years, had pneumonia seven weeks before with relapse and return of symptoms after initial improvement. Since then, he complained of pain in the left chest on breathing, moderate cough and profuse sputum. Examination revealed diminished expansion of the left chest, dullness at the left base, distant breath sounds in this area and numerous medium-sized crackling râles. Sputum examination was negative for tubercle bacilli on numerous occasions. Roentgen ray examination showed evidence of pleural thickening and adhesions at the left base. Thoracentesis resulted in a dry tap. Examinations of the chest, including roentgenologic examination, previous to the pneumonia, had revealed normal lung findings. The patient had contracted syphilis four years before and one year before had had syphilitic meningitis. The Wassermann test of blood and spinal fluid was strongly positive (4+) on several occasions, that of the blood ± on the last occasion. He had had antisyphilitic treatment at intervals. Diagnosis: Unresolved pneumonia with preëxisting syphilis.

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THE THERAPEUTIC USE OF DIGITALIS.*

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There is no other known drug so potent as digitalis in the treatment of certain disturbances of cardiac function. Equally true is the fact that its powers are strictly limited. Its successful employment depends on the knowledge of its possibilities and limitations, how it may be expected to modify the behavior of the functionally altered heart. It is not the sovereign remedy for heart disease as it has been called sometimes; strictly speaking, it can scarcely be regarded as a remedy for heart disease, in spite of the fact that it is remarkably effective in easing some of the burdens imposed by heart disease on the work of that organ.

The above distinction is fundamental, if we are to assign digitalis its proper place in treatment. When dealing with a failing heart, we are not relieved of the responsibility for searching out rigorously the underlying causes of that failure and retracing the course of events so far as possible to the very beginnings of disease. It is not necessary to say that digitalis does not cure faulty habits of life nor infected gall bladders, nor does it materially influence the bad effects of these and the like on the heart. Even when—as is too frequently the case—our therapeutic efforts are limited to the symptomatic treatment of heart failure, our attention should be directed first toward securing comfort, rest, satisfactory sleep, adequate functioning of the gastrointestinal tract, and whatever else may be done to ease the burden on the heart.

In this discussion, no further attention will be paid to other appropriate procedures in the treatment of heart disease, the remarks being limited strictly to a consideration of the therapeutic uses of digitalis. The main part of the subject may be divided conveniently into two headings: (1) The treatment of abnormal rates and rhythms, and (2) the treatment of heart failure with normal type of cardiac mechanism.

Abnormal Rates and Rhythms. *Simple Tachycardia.* Ever since Withering called attention to its diuretic properties, digitalis has also enjoyed a reputation for slowing the pulse. Some of the earlier observers called attention to the fact that this action was most marked in cases with rapid and irregular pulse. It was not until auricular flutter and fibrillation were recognized clinically, that its peculiar potency in these conditions was distinguished from its

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effects in other forms of rapid action. Its reputation for slowing the heart was, and by many still is, unwarrantedly extended to the normally beating heart.

There is no doubt that digitalis slows the normally beating heart in a certain proportion of cases. In adults, the amount of this slowing is usually insignificant. In children and adolescents, with their more responsive inhibitory mechanisms, the effect may be much more marked. Well-conducted studies on postrheumatic tachycardia in children have shown decisive fall in pulse rate and clinical improvement attributed to digitalis. If fever is still present, these beneficial results are not obtained.

In adults with preserved compensation, the attempt to control simple tachycardia by digitalis is almost certainly doomed to failure. If the heart rate falls during digitalis administration, adequate analysis of the case will usually show some other cause for the slowing.

When simple tachycardia occurs in decompensated hearts, one sometimes sees an abatement of the rapid rate coincident with restoration of compensation during digitalis therapy. In such cases, it is probable that the reduction of rate is dependent on improvement in the strength of the heart beat and the general circulation, and thus indirectly to digitalis.

The Arrhythmias. Before discussing the use of digitalis in the treatment of abnormal cardiac mechanisms, it is worth noting that under suitable conditions it is able to cause the following forms of arrhythmia: Sinus arrhythmia, sinoauricular heart block, depressions of sinoauricular function leading to ventricular escape and auriculoventricular nodal rhythm, extrasystoles, paroxysmal tachycardia (particularly ventricular tachycardia both of conventional and bizarre types), minor and major grades of heart block including complete block, and pulsus alternans. It is also capable of converting auricular flutter to fibrillation and the evidence at hand warrants the suspicion that in hearts with normal mechanism predisposed to fibrillation, digitalis may precipitate fibrillation.

Disturbances of Sinus Rhythm. Sinus arrhythmia, ventricular escape, auriculoventricular rhythm, and sinoauricular block require treatment only when the cardiac action becomes extremely slow and the circulation disturbed on that account. Since the aim of treatment is to stimulate the activity of the sinus node, digitalis is not only of no value but is contraindicated.

Extrasystoles. As stated above, digitalis is capable of exciting extrasystoles and this is by no means a rare by-product of its action, especially when given in full dosage. Nevertheless, the initial presence of extrasystoles should never be regarded as a contraindication to its use. It is scarcely to be recommended for the express purpose of suppressing extrasystoles, although occasionally they will disappear under its influence.

Auricular Fibrillation. It is in the treatment of auricular fibrillation that digitalis finds its greatest field of usefulness. Its efficacy in this condition depends, as Lewis has emphasized, on a sedative or depressing rather than a stimulating action. This depressive action is exerted on the transmission of impulses through the junctional tissues. Four hundred to 600 or more impulses per minute from the fibrillating auricles bombard the junctional tissues and if no block is present, 140 to 200 may be expected to pass and stimulate the ventricles to contraction. By the proper dosage of digitalis, blocking of these impulses can often be controlled to within 10 beats per minute of the ventricular rate desired. This control of ventricular rate should be the sole aim of digitalis therapy in auricular fibrillation. When the proper rate is obtained, the dosage given has been adequate, no matter how much or little this may be.

When the patient is desperately ill as a result of heart failure precipitated by fibrillation with rapid ventricular rate, treatment according to the principles laid down by Eggleston may be life-saving. If small doses are given, several days instead of several hours are required before digitalis effects are manifest, and the patient may die of heart failure during the interim. Where no emergency exists—and this is true of the great majority of cases even in hospital-ward practice—slower methods of administration are justifiable and except in the hands of the most expert, preferable.

Most discussions of digitalis therapy dismiss the subject rather summarily once the rate has been brought within bounds, but this is really only the beginning of treatment. As a matter of fact, it is not always possible to control the rate properly during the first administration, due to the development of toxic symptoms, and it may be necessary to interrupt treatment and begin again. There are few if any cases, however, in which eventually the rate cannot be brought to the desired level.

The next step is to try to discover the optimum ventricular rate at rest. In my experience this is usually between 70 and 80 beats per minute although a few patients do better with a rate between 60 and 70. On the other hand, fibrillators with aortic regurgitation rarely are at their best when the rate is slow and it may be necessary to maintain them in the neighborhood of 90 beats per minute.

Having found the optimum rate, the next problem is to maintain it. This is usually not so difficult while the patient is at rest or on measured amounts of activity. Under such circumstances, the amount of digitalis required to hold the rate practically constant shows little variation from time to time, unless infection or some other physical or mental upheaval occurs. In different patients, the amount required usually ranges from ½ to 2 gr. of a good powdered leaf daily. As activity is resumed, slightly larger dosage may be necessary.

An intelligent patient can often be taught to regulate his own dosage satisfactorily. The optimum rate and the approximate dosage required to maintain it having been ascertained, powdered digitalis leaf is given daily in amount slightly less than the requirement. The patient is taught to count his heart rate by palpating the apex impulse, lying on the left side if necessary. The count is made before arising in the morning. If the heart rate before arising is less than the lower limit of the optimal range, no more than the regular daily dosage is taken. If it is within the range, one extra dose of ½ gr. is added. For example, if a patient has an optimum rate of between 70 and 80 beats per minute and his daily requirement of digitalis is between 1 and 1½ gr. of powdered digitalis, 1 gr. is given every day. On such mornings as the heart rate is above 70, an additional ½ gr. pill is taken, but if the rate is under 70, this dose is omitted.

The above plan is satisfactory, provided the patient is capable of counting his apex rate accurately. It is to be used in patients who are unable to see their physician at frequent intervals.

I have emphasized the importance of maintaining the optimum rate during fibrillation, since this is the most frequent source of error in treatment. The usual errors are inadequate dosage and intermittence of treatment. Overdosage seems to be far less common.

If compensation has not been restored by maintaining the ventricular rate somewhere between 60 and 90 beats per minute, or if compensation fails while the rate is being so maintained, the indication is not for larger dosage of digitalis, since it will do harm rather than good. The indication is to lessen the work required of the heart by putting the patient to bed if necessary.

The impression seems to be held by many that digitalis has a tendency to abolish auricular fibrillation. This view is erroneous; when normal rhythm is restored during digitalis administration, the change occurs not because of, but to a certain extent, in spite of the drug. Occasionally it may bring about regular beating by causing complete dissociation, but the auricular fibrillation remains. Frequently as it slows the ventricular action, it eliminates the highly premature and weak beats, so that the action is less irregular and may be mistaken by those with undeveloped sense of rhythm for regular beating.

Auricular Flutter. The mechanism and general behavior of auricular flutter are in most respects similar to auricular fibrillation and with one important exception, the treatment is similar. The exception is due to the fact that in most cases of auricular flutter treated vigorously with digitalis, flutter will be converted to fibrillation. If digitalis treatment is then abruptly stopped, many will spontaneously revert to normal rhythm. Advantage may be taken of this fact, and according to the consensus of opinion of workers

in this field, at least 50 per cent may be restored to normal rhythm. Some cases cannot be converted from flutter to fibrillation, toxic symptoms or complete block intervening, while others can be converted to fibrillation, but will not revert to normal rhythm. Patients belonging to the last group may remain in fibrillation after digitalis administration, or revert to flutter.

Paroxysmal Tachycardia. The general opinion, as obtained from literature, seems to be that digitalis is of no value in the treatment of auricular or ventricular tachycardia, neither as to the termination of paroxysms nor their prevention. It has been incriminated as a cause of ventricular tachycardia. My experience with the clinical types of auricular tachycardia in which frequently recurring paroxysms disturb the normal rhythm is favorable to digitalis treatment. It is at least worthy of a trial in cases which do not respond favorably to quinidin.

It is thought best not to use digitalis during the early stages of a paroxysm of auricular flutter or fibrillation, as it is suspected of having an influence in the direction of prolonging paroxysms. While the truth of this contention is not established, there are good reasons for believing it may be so. It is only when cardiac failure threatens or the paroxysm has lasted long enough to arouse suspicion of the establishment of chronic arrhythmia that digitalis should be used.

There is little evidence to indicate that digitalis is of value in suppressing the recurrence of paroxysms of flutter or fibrillation in patients subject to these disorders.

Heart Block. In general, the use of digitalis should be avoided in patients with incomplete heart block, even minor grades of block. It is often easy to bring about complete dissociation by moderate dosage of digitalis in patients who initially had no more than slight delay in the transmission of the excitatory process. I have seen one such case in which complete block persisted and similar cases are recorded in the literature. This undesirable handicap to the cardiac efficiency should naturally be avoided if possible.

Permanent complete block offers no contraindication to the use of digitalis. It may be employed in the presence of heart failure just as in patients with normal mechanism. Some observers have reported a speeding up of the slow idioventricular rate under its influence, an effect that should be highly desirable. Other workers have failed to obtain this result.

Digitalis may be employed to prevent Adam-Stokes syndrome provided such attacks are dependent on changes back-and-forth between high-grade incomplete block and complete block and slowness of the idioventricular center in picking up its rhythm. Under such circumstances, if complete block is established and maintained by digitalis, the Adam-Stokes syndrome is suppressed.

Heart Failure with Normal Type of Cardiac Mechanism. About fifteen years ago, following the differentiation of auricular flutter and fibrillation, Mackenzie and Lewis both denied that digitalis was of importance in the treatment of heart failure when the mechanism was normal, although Mackenzie did admit that it had some value in removing cardiac dropsy. These remarkable views, expressed by such distinguished authorities, views that seemed contrary to both laboratory and clinical experience, led to much more careful and better controlled clinical research on this subject than had been available previously. As a result of these researches, our knowledge has been greatly extended, so that statements with respect to clinical digitalis effects may be made with much greater confidence than was possible ten years ago.

It has been clearly established that in the familiar form of severe congestive heart failure with its attendant fluid collections, digitalis may not only be effective but spectacular in its results. Diuresis occurs with removal of collections of fluid from the body and marked restoration of the circulation follows.

Success in the treatment of these cases depends on adequate dosage of the drug. Exceptionally improvement, notably diuresis, begins comparatively early. This should be the signal for proceeding slowly, since thorough digitalization may lead to suppression of the diuresis. In most cases however, therapeutic effects do not manifest themselves until full dosage has been administered, so that the margin between therapeutic and toxic dose is small. Failure of appetite should be the warning signal and the development of nausea an imperative indication for diminishing or temporarily discontinuing the drug. Dilatory observance or neglect of this rule in these very ill patients may lead to unpleasant results and the possibility of hastening death.

Christian has pointed out the fact that in the first attack of heart failure digitalis may be very effective but in subsequent attacks it gradually loses its power until finally it becomes totally ineffective. This is probably not due in any way to habituation to the drug but to progressive deterioration of the myocardium so that it is no longer capable of responding. Such a condition of the myocardium is doubtless not infrequently present during the first attack of failure and accounts for the fact that digitalis is sometimes totally ineffective.

Digitalis is of especial value in the treatment of elderly patients with a more or less stationary condition of myocardial weakness that involves them from time to time in mild attacks of failure. In these patients, the progressive lessening in value of digitalis is not so manifest and the drug may be of value in clearing up many attacks.

One of the unsettled problems is what to do with respect to

continuing digitalis therapy after the patient has been rescued from decompensation. The indication is by no means so clear as in the case of auricular fibrillation. Many clinicians favor continued administration, keeping the dosage below the toxic level, believing that this procedure helps to strengthen the cardiac action and prevent future breakdown. Others prefer to employ the drug only in the presence of actual failure. Probably all will agree that if cardiac function improves to a point where failure no longer threatens, digitalis is not required. The general tendency is to employ it in cases regarded as verging on failure and this procedure seems to be of value in warding off a breakdown.

In heart failure of noncongestive types, digitalis has not been found nearly so valuable. Its use is not contraindicated, but failure to obtain satisfactory results will be frequent. In my own experience and that of many others, it is of no value in the treatment of the symptom complex, angina pectoris. There is no clear-cut evidence that it averts the individual attacks nor mitigates their severity.

Type of Cardiac Lesion. It is generally stated that digitalis is more effective in the presence of mitral-valve disease than aortic regurgitation. Many of the older writers cautioned against its use in aortic regurgitation. There is no doubt that heart failure with associated aortic regurgitation is in general much more refractory to treatment than mitral disease, but some patients are doubtless benefited by digitalis and the caution against its use is not justified. Cases of myocardial disease without valvular defect appear to react as well as the mitral cases.

The view has been propounded that digitalis should act especially well in mitral stenosis because by producing delay in As-Vs intervals, the left auricle is given more time to pump blood into the left ventricle and so facilitate filling of that chamber. Clinical data do not seem to confirm this view.

Since digitalis is capable under certain circumstances of laboratory experiment of constricting coronary vessels, apprehension has been expressed regarding its clinical use in the presence of actual or suspected coronary artery disease. This apprehension is apparently without foundation and the presence of coronary disease is not to be regarded as a contraindication to the use of the drug.

Blood Pressure. The action of digitalis on blood pressure depends on whether or not heart failure is present. The various forms of hypertension not associated with heart failure are usually little influenced by digitalis. The same is true of hypotension without associated heart failure, and the practice of treating such forms of hypotension with digitalis is ineffective.

During treatment of heart failure with digitalis, marked variations of blood pressure may be observed. It is universally recognized that in heart failure, the pulse pressure tends to be lessened. This

may be brought about by elevation of the diastolic pressure without much change in the systolic, or by fall in the systolic pressure with little change in the diastolic. In any event, the systolic and diastolic figures tend to approach. It is not so generally recognized, however, that heart failure may lead to elevation, even marked elevation, of both systolic and diastolic pressures, probably as a result of a vasomotor compensatory mechanism attempting to preserve the circulation. Thus as compensation is restored, blood pressure tends to return to the normal for the individual under consideration. Although there are many variations, high systolic pressures tend toward reduction, and low pressures toward elevation. There is a marked tendency toward lowering of diastolic pressure and increase of pulse pressure.

How much of these changes in pressure is attributable to digitalis directly and how much to increased vigor of the heart beat and consequent relief of vascular compensatory mechanisms is, so far as our present discussion is concerned, an academic question. The point to remember is that the levels of blood pressure should not be regarded as of importance with respect to the choice of digitalis as a therapeutic agent in heart disease.

The Thyroid Heart. There is no doubt that the most effective treatment of a heart overstimulated by the thyroid gland lies in the proper control of the thyroid. Nevertheless, it is sometimes necessary to support or improve the circulation so that appropriate treatment of the thyroid can be instituted. Statements in the literature to the effect that digitalis is of no value in the treatment of heart failure due to hyperthyroidism are incorrect.

For several years, Dr. Edward Rose and I have been carrying out studies along these lines (unpublished) and our main conclusions to date with regard to digitalis are that its action in heart failure due to hyperthyroidism are similar to its effects in other forms of heart failure. The cardiac response to treatment is usually not so prompt in the hyperthyroid heart, tolerance to the drug may be greater and comparatively larger dosage may be required to produce results. In auricular fibrillation, the ventricular rate can usually be controlled and the state of the circulation correspondingly improved if treatment is persisted in and appropriate dosage of digitalis given.

Infections. Digitalis is almost universally used in this country in the treatment of severe general infections, particularly penumonia, with the idea of supporting or stimulating the heart. There is very little dependable evidence to indicate whether or not this practice is beneficial. The most often quoted observations favoring this use of digitalis are those of Cohn and Jamieson who carefully studies 105 cases of pneumonia of which 49 received digitalis and 56 served as controls. These observers found that approximately 10 per cent of their patients developed auricular fibrillation and among these they believe digitalis may be beneficial or even life-saving.

They therefore recommend routine digitalization of patients with pneumonia. This work coming just before American participation in the World War doubtless had an effect in the promulgation of that remarkable order to medical officers in the A. E. F. detailing the dosage of digitalis to be given all patients with pneumonia.

Two objections may be raised regarding the general applications of the conclusions of Cohn and Jamieson. In spite of the findings in their series, in a large group of cases of pneumonia, auricular fibrillation is found to be a comparatively rare complication except in the dying heart, when no treatment may be expected to have value. Consequently the value of digitalis in this direction will be of very limited scope. Furthermore, Robinson has raised the question as to whether or not digitalis may have a tendency to excite fibrillation in these hearts. The value of digitalis in pneumonia and other infections must therefore still be regarded as open to question.

In the treatment of infections such as rheumatic fever and diphtheria which frequently produce minor grades of heart block, the use of digitalis may convert minor block to high-grade block, thus impairing the efficiency of the circulation and defeating the purpose for which it was employed.

Digitalis and Surgery. The principles of digitalis therapy are no different in surgical than in medical cases, although certain special problems sometimes arise in connection with operations.

Some writers have recommended routine preoperative digitalization irrespective of the state of the heart as a preliminary to certain types of prolonged or arduous operations, while others have condemned this practice. Although there is abundant proof that overdosage with digitalis will impair the efficiency of any heart, there is no proof that so-called therapeutic dosage either increases or decreases the capacity of the healthy heart. The various pharmacologic demonstrations of digitalis actions on the circulation do not supply the answer to this question. Until such evidence is forthcoming, digitalization of the healthy heart is not to be recommended, no matter how serious an operation is contemplated.

In the case of patients with diseased hearts who require surgical operation, the use of digitalis is similar to that practised in purely medical cases. In the presence of auricular fibrillation, the ventricular rate is carefully controlled before operation. Under such conditions, it usually holds remarkably well during operation. Patients who develop attacks of paroxysmal fibrillation or flutter with rapid ventricular rate should receive at least 75 per cent of the calculated therapeutic dosage before operation, since such attacks are very liable to develop during or after operation. This amount of digitalis tends to keep the ventricular rate within bounds, should a paroxysm of flutter or fibrillation develop, and thus helps to preserve cardiac efficiency.

When the cardiac mechanism is normal but decompensation is present or threatened, every effort should naturally be made to build up the cardiac reserve before operation. Digitalis has a place in this treatment, particularly if congestive phenomena are present. It is remarkable how well many of these patients undergo operations, particularly if local anesthesia can be employed.

Postoperative circulatory collapse with low blood pressure, thready rapid pulse, and all the other familiar phenomena is too well known to need description here. Whether it be due to shock, hemorrhage, or sepsis, the failure is usually at the opposite end of the circulatory system, the vasomotor control, rather than the heart, and therapeutic efforts should be exerted in that direction rather than toward the heart. The rather general practice of giving digitalis is ineffective even when appropriate dosage is employed. The customary small hypodermic or intramuscular injections have little effect beyond the production at times of abscesses at the site of injection. I have twice seen extensive infections started by digitalis injections which made no small contributions to the death of the patients.

Conclusion. Success in the use of digitalis depends on recognition of the indications for its use and the employment of proper dosage.

A STUDY OF THE COMPARATIVE VALUE OF TESTS OF RENAL FUNCTION IN A GROUP OF CASES OF MILD OR SUSPECTED NEPHRITIS.

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In this study a group of 52 patients with mild or suspected nephritis has been taken for the purpose of determining, if possible, which of the more commonly used functional tests are the most sensitive or dependable. The relation of the day and night urine volume and specific gravity, the blood urea nitrogen, the phenolsulphonephthalein excretion, the urea concentration test (MacLean), the urea concentration index (McIntosh) and a slight modification of the urea concentration factor (Harrison) have been applied to each of the cases. With the exception of the urea concentration index, all of these tests have been used extensively heretofore, but no comparative studies of all the tests in a single group of patients have appeared in the literature.

The renal function tests most commonly used, at least in clinics in the United States, are the two-hour renal test of Hedinger and

Schlayer[1] as modified either by Christian or Mosenthal, the phenolsulphonephthalein test of Rowntree and Geraghty, and a determination of the nonprotein or urea nitrogen of the blood. Within the past few years, tests to determine the capacity of the kidney to concentrate urea have been advocated from several quarters as a better index, as the added urea places the kidney under a strain and brings more of the organ into service. The concentration test was originally introduced by MacLean, and de Wesselow[2] in 1920. MacLean[3] has now used the test in over 10,000 cases with varying degrees of nephritis and believes that a concentration of urea in the urine, either during the first, second or third hour, of less than 2 per cent after the oral administration of 15 gm. of urea, indicates renal insufficiency, providing the volume of the specimen is less than 120 cc. In 1922, Addis[4] suggested a rather complicated and prolonged urea test, which he believed measured the relative amount of secreting tissue in the kidneys; he employed from 15 to 30 gm. of urea according to the grade of impairment. Jones and Cantarow[5] compared the urea concentration test with the 'phthalein test and the blood chemistry in a series of 30 patients with varying grades of nephritis. They used a modification of the MacLean test comparing the percentage of concentration in the urine before and after the ingestion of 15 gm. of urea. They allowed, however, a maximum urine volume of 150 cc. after the administration of urea, instead of 120 cc. as used by MacLean, and they permitted more water, which may have made their results lower. They concluded that the variation of urea concentration, thus determined, offered a better measure of renal damage than the response to urea alone. They noted that the 'phthalein excretion failed to indicate the probable renal impairment in some instances. Their test seems rather complicated for a routine procedure.

Harrison,[6] in 1922, published results with the use of the urea concentration test. He concluded that if the concentration of urea in the first-, second- or third-hour specimens of urine after the administration of 15 gm. of urea exceeded 2.5 per cent, probably no further information of clinical value would be gained by the determination of the blood urea. He further stated that if the concentration lay between 2 and 2.5 per cent, it would be safer to determine the blood urea, so that the factor of urea concentration might be estimated. The factor suggested was:

$$\frac{\text{Milligrams urea per 100 cc. urine passed during the third hour}}{\text{Milligrams urea per 100 cc. blood obtained in middle of third hour}}$$

He studied 40 cases that were, with one exception, potentially nephritic, with a concentration of urea in the second or third hour of at least 2 per cent, and found a wide variation of the factor: 18 to 72. He cautioned that excessive diuresis vitiated the results

and believed that a urine volume exceeding 100 cc. during the second hour should not be used.

Mills and Rabinowitch[7] compared the urea concentration factor estimated during the first hour with that of the second hour, after the administration of 15 gm. of urea in 100 cases and concluded that the second hour gave the higher value, and therefore recommended its use.

Rabinowitch[8] compared the blood urea nitrogen, urea concentration test and urea concentration factor, and the 'phthalein excretion in 200 patients with varying grades of nephritis. He concluded that the urea concentration factor is the most sensitive test. In a later communication, he[9] found that the urea concentration factor showed impairment of renal function in 94 per cent of the 284 cases studied, but of these, only 44 per cent showed nitrogen retention.

Black[10] studied a group of 15 ambulatory patients with arterial hypertension who had a concentration of blood urea nitrogen of less than 20 mgm. per 100 cc., comparing the two-hour renal test, 'phthalein excretion and the urea concentration test. Seven had a night urine volume of more than 400 cc., 7 had a 'phthalein output of less than 50 per cent, and only 3 had a urea concentration in the second hour's urine that was over 2 per cent after taking 15 gm. of urea. He concluded that the urea concentration test had some merit.

Christian and O'Hare[11] found that a fasting blood urea nitrogen in excess of 15 mgm. per 100 cc. should be regarded with suspicion, in the absence of cardiac passive congestion. They believe that the test is of great value in the study of any renal case, especially in following the effect of diet and in the quick and accurate diagnosis of uremia. The 'phthalein test in their hands has proven satisfactory and they regard any reading that is over 40 per cent for 130 minutes as normal, but state that values under that point do occur when there is heart failure only. It is their judgment that the two-hour renal test is the most delicate and recommend its use in cases of suspected nephritis who have normal blood urea nitrogen and 'phthalein readings. It has been their experience that a night urine volume that exceeds 600 cc. and has a specific gravity of less than 1.018 usually indicates chronic nephritis, but that the further increase in the night volume is not necessarily an important prognostic sign.

Jones[12] likewise believes that the two-hour renal test demonstrates lesser degrees of renal damage, and that nitrogen retention does not occur until considerable impairment is present. He states that an increase in blood nitrogen is usually present when the 'phthalein output is less than 40 per cent in two hours. In the carrying out of the two-hour test, he recommends that the night urine be collected from three hours after the evening meal to the next morning, and that no fluid should be allowed during the night;

under such conditions, the ratio of the day to the night urine volume, normally, is three or four to one, and the specific gravity of the night urine should be at least 1.018. He further states that some normal persons have a night urine of 750 cc.

Foster[13] states that the 'phthalein test is quite useless until renal degeneration is well advanced. It is likewise his experience that the early cases do not show any fixation of specific gravity.

Rabinowitch,[14] studied the night urine volume, urea concentration test, and 'phthalein excretion in 50 cases, who for the most part had mild or questionable renal lesions. He concludes that the information gained from the night urine volume parallels that from the urea concentration test, but that both give only qualitative information. It is observed in his report that only 2 cases having a 'phthalein elimination under 40 per cent failed to show a concentration of urea in the second hour of less than 2 per cent, but that several who had low concentrations had 'phthalein percentages well above 40 per cent. He accepted 400 cc. as the maximum normal night urine volume. He did not state whether in all the cases the urine collected during the second hour had a volume of less than 120 cc., although he gave the urea in 100 cc. of water.

Mosenthal,[15] who has had a wide experience in the use of the two-hour test, now states that nocturnal polyuria should not usually be assumed unless the volume exceeds 750 cc. Also, he considers the specific gravity very important and believes that some time during the day it should reach 1.018 or 1.020. He finds the two hour renal test very satisfactory to carry out on ambulatory patients.

Hubbard[16] made a comparative study of the urea nitrogen of the blood and the excretion of 'phthalein in a series of about 300 patients. He found that an average concentration of 18 mgm. of urea nitrogen corresponded to a dye elimination of 50 to 55 per cent. Hubbard[17] also studied the two-hour renal test and the 'phthalein test in a group of cases. He found that fixation of specific gravity did not usually occur until the dye excretion was less than 25 per cent, and that increase in the night urine volume paralleled decrease in the 'phthalein value, between 25 and 60 per cent.

Addis and Foster[18] gave a group of normal people fairly large doses of urea, sodium chlorid, and acid sodium phosphate, both separately and combined. He compared the specific gravity of the urine with the amount of these substances eliminated under strictly standard conditions. He concluded that not even an approximate idea of the excretion of solids could be determined from the results, and that therefore, specific gravity tests are no index to the amount of secreting tissue in the kidney.

Addis and Watanabe[19] found that a change of diet from mainly carbohydrate to mainly protein fat increased the blood urea concentration by from 58 to 250 per cent in normal individuals. Also in a group of 22 normal subjects on a constant diet variations from

22.5 to 60 mgm. of urea (not urea nitrogen) were found in the fasting blood. One hundred and six estimations were made.

In a recent communication, Fishberg[20] has suggested a somewhat different conception of renal function. He believes that the kidney functions as a unit no matter what the structural change may be, and that a lowering of the maximum concentration for each of the urinary constituents is the index of function. He brings up the point that each constituent has a different concentration ratio (between blood and urine) and that the reason for the lack of retention of some substances, such as calcium, chlorid, and so forth, is that their ratio is too low for slight differences to be detected. He has employed a modification of the dilution and concentration test of Volhard and believes that a maximum specific gravity that is less than 1.020 is indicative of renal impairment but no matter how extensive this impairment may be, the specific gravity (maximum) never falls below 1.010. He differentiates between compensated renal hypofunction, where a lessening of maximum concentration occurs without retention of the urine constituents in the blood, and uncompensated renal hypofunction, where both occur. He further states that when selective retention occurs in cases of nephritis, it is caused by some extra-renal factor.

Addis and Shevky[21] studied the specific gravity of the night urine in a group of 75 normal students who had been on fluid restriction during the day. They found an average specific gravity of 1.032, with a standard deviation of ± 0.00281.

McIntosh[22] has recently introduced the index of urea concentration and has used it with satisfactory results, especially in cases of acute nephritis. His index has the following formula:

$$\frac{\text{urine urea (grams per liter)}}{\text{blood urea (grams per liter)}} \times \sqrt{\frac{\text{urine volume (cc. per hour)}}{\text{body weight (kilograms)}}}$$

He found the normal range to lie between 35 and 75.

Archer and Robb[23] developed a urea tolerance test to be used in connection with the urea concentration test. Their normal standard was based upon the study of four subjects whose fasting blood urea varied between 28 and 38 mgm. per 100 cc. In these normal subjects the maximum rise—5 to 15 mgm.—occurred in thirty to sixty minutes after the ingestion of 15 gm. of urea, and the recovery back to the normal level was nearly complete in 120 minutes. They found a delayed recovery period in 11 of 12 persons who had some definite renal disease, while the urea concentration test showed a disturbance in only two. It was noted that the majority of their cases who had a urea concentration above 2 per cent and showed a delayed recovery period, had heart failure or acute nephritis. Harrison, however, found the blood urea two and a half hours after the ingestion of 15 gm. of urea from 37 to 133 mgm. in a group of hospital patients who had a urea concentration test, above 2 per cent.

TABLE I.

Number.	Sex.	Age.	Blood pressure.		Urinalysis.									'Phthalein per cent 130 minutes.	McIntosh index of urea concentration.	Fifteen grams urea.			Blood uric acid (fasting).	Rating of cases.	Remarks.
					Albumin.	Casts.		Cells.		Twenty-four hour urine.						Blood urea nitrogen	Urea concentration 2d hour per cent (Mac Lean)	factor (Harrison)			
										7 A.M.–9 P.M.						fasting		U. urea			
										9 P.M.–7 A.M.						2d hour		B. urea			
			Systolic.	Diastolic.		Hyaline.	Granular.	Red.	White	Volume cc.	Sp. gr.	Day night urine volume ratio.									
Chronic nephritis with hypertension.																					
1	M.	24	145	100	++++	+	○	+	+	1500	1.004	2.14:1	46	24.7	16.1	1.9	34.3	3.6	+	Rapid pulse, thyroid adenoma, normal metabolism.
										700	1.009				25.9					
2	M.	30	160	85	++++	+	+	○	○	660	1.016	0.86:1	55	23.5	14.7	1.26	24.74	5.33	+	Duration 8 years.
										840	1.014				23.8					
3	M.	32	170	100	++	○	○	○	○	640	1.030	0.98:1	68	30.52	15.4	1.55	25.86	3.6	+	Occasional edema, diabetes.
										650	1.015				28.0					
4	F.	38	140	75	+	+	+	○	○	1380	1.009	1.35:1	49	12.8	17.5	0.85	13.84	2.54	+	High blood pressure for several years.
										1025	1.011				28.7					
Chronic nephritis with edema.																					
5	F.	47	130	90	+	++	+	○	○	1070	1.010	1.36:1	42	18.8	17.5	1.61	20.3	....	+	Edema of legs following diabetic coma.
										1460	1.011				37.1					
6	F.	13	95	70	++	+	+	○	○	820	1.007	1.91:1	54	47.8	15.4	2.66	27.0	?	?	Moderate edema.
										430	1.012				46.1					

7	F.	10	100	75	+++	+	+	+	+	540 320	1.013 1.012	1.68:1	29	19.5	24.0 53.0	1.7	15.0	....	+	Died from diphtheria and uremia. Slight edema.
8	M.	38	112	82	+	O	O	O	O	880 1000	1.009 1.020	0. 9:1	64	53.6	11.9 25.1	1.8	33.53	....	?	No edema at time of tests.
9	M.	15	120	70	+	+	O	O	O	1620 720	1.010 1.012	2. 3:1	54	26.8	12.6 26.6	2.2	38.2	2.76	?	No edema at time of tests.
										Chronic nephritis with edema and hypertension (mixed).									
10	F.	59	175	92	++	+	+	O	O	475 850	1.012 1.012	0. 6:1	31	8.9	28.7 48.9	1.38	13.2	....	+	Mild diabetes; edema disappeared with ammonium chloride.
11	M.	22	182	120	++++	+	++	occa.	+	630 1060	1.016 1.011	0. 6:1	Trace	6.45	59.4 89.3	0.91	5.0	3.9	+	On high protein diet. Duration 7 years.
										Chronic arterial hypertension.									
12	F.	53	170	95	+	O	O	O	O	1420 485	1.010 1.018	2.92:1	62	.....	22.4 30.8	2.58	39.14	2.22	O	Diabetes.
13	F.	55	165	90	+	O	O	O	O	1820 800	1.011 1.013	2.25:1	58	34.0	14.7 24.5	2.43	45.8	3.45	O	Mild diabetes and psychoneurosis.
14	F.	50	160	95	O	O	O	O	O	1875 460	1.008 1.014	4. 1:1	62	24.6	19.5 35.6	2.9	38.1	...	?	Diabetes.
15	M.	50	180	90	+	+	O	O	O	780 360	1.017 1.017	2. 2:1	47	29.6	21.7 32.2	1.46*	21.2	....	?	Arteriosclerosis.
16	M.	58	176	76	Spt. †	+	O	O	O	495 275	1.030 1.030	1. 8:1	64	23.3	23.8 31.5	3.7	56.5	....	?	Obesity.
17	M.	38	145	105	Spt.	O	O	O	O	2090 500	1.008 1.012	5. 8:1	64	49.0	14.7 30.1	2.8	44.1	3.1	O	Diabetes.
18	F.	57	200	90	+	+	O	O	O	500 260	1.023 1.021	1.92:1	46	31.6	18.9 34.1	2.8	33.9	4.0	O	Hyperthyroidism arteriosclerosis.

TABLE I.—(*Continued.*)

Number.	Sex.	Age.	Blood pressure.		Urinalysis.									Phthalein per cent 130 minutes.	McIntosh index of urea concentration.	Fifteen grams urea.			Blood uric acid (fasting).	Rating of cases.	Remarks.
					Albumin.	Casts.		Cells.		Twenty-four hour urine.						Blood urea nitrogen fasting / 2d hour	Urea concentration 2d hour per cent (Mac Lean).	factor (Harrison) U. urea / B. urea			
										7 A.M.–9 P.M.											
										9 P.M.–7 A.M.											
			Systolic.	Diastolic.		Hyaline.	Granular.	Red.	White.	Volume cc.	Sp. gr.	Day night urine volume ratio.									
										Chronic arterial hypertension (continued).											
19	F.	44	145	90	+	+	○	○	○	630	1.014	0. 9:1	75	43.50	11.9	3.4	55.3	3.6	○	Gall bladder disease.
										700	1.019				33.6					
20	F.	45	170	110	+	○	○	○	○	750	1.013	2. 8:1	52	34.42	13.3	2.0*	30.2	3.2	○	Toxemia of pregnancy twice, diabetes.
										270	1.018				30.8					
21	F.	67	170	100	+	+	○	○	○	1080	1.006	3. 6:1	55	17.4	12.0	2.2	31.8	4.3	?	Retinal arteriosclerosis, cataracts.
										300	1.019				33.6					
22	F.	49	258	128	+	○	○	○	+	500	1.018	0.54:1	50	28.0	16.0	1.73	28.2	2.86	+	In hospital because of hallux valgus.
										920	1.010				28.7					
23	F.	50	190	125	+	○	○	○	○	1210	1.008	1.64:1	54	35.0	15.4	2.25	32.6	3.6	?	Nearly symptomless.
										740	1.008				32.2					
24	M.	51	160	80	+	+	○	○	○	1330	1.009	0.82:1	62	45.12	12.6	2.11	48.5	....	?	Diabetes.
										1610	1.008				20.3					
25	F.	57	215	120	+	+	○	○	○	520	1.015	0.72:1	41	18.8	17.5	3.22	55.0	....	?	Old hemiplegia, diabetes.
										720	1.010				27.3					

									720	1.010				27.3					

Heart failure (predominating).

26	F.	32	122	80	+	+	○	○	○	1620	1.012	2. 2:1	33	10.5	25.9	2.7	34.3	....	?	Chronic myocarditis.
										740	1.010				36.3					
27	F.	43	150	95	Spt.	+	○	○	○	1490	1.005	1.13:1	26	29.8	22.4	2.3	30.9	....	+	Diabetes, arteriosclerosis, gastric ulcer.
										1320	1.011				35.0					
28	F.	36	122	70	Spt.	○	○	+	+	540	1.010	0.71:1	46	18.82	23.8	1.6	19.9	3.9	+	Mitral stenosis, chronic myocarditis.
										755	1.006				37.1					
29	F.	57	170	104	+	○	○	○	+	520	1.009	0. 9:1	18	14.4	19.0	1.35	24.8	....	+	Hypertension, auricular fibrillation.
										580	1.014				25.4					
30	F.	58	155	110	+	occa.	○	○	○	260	1.017	0.54:1	44	17.68	18.1	2.00	28.9	....	+	Obesity, hypertension, syphilis.
										480	1.011				32.2					
31	F.	58	105	70	Spt.	○	○	○	○	515	1.007	0.27:1	40	31.8	15.4	2.11	36.1	....	+	Chronic myocarditis, auricular fibrillation.
										1900	1.011				27.3					

Arterial hypertension progressing into chronic nephritis.

32	M.	47	200	120	++	+	++	○	○	600	1.012	1. 1:1	44	29.2	21.7	2.23	31.8	3.5	+	Hypertension 10 years retinal hemorrhages.
										540	1.009				32.8					
33	F.	52	190	80	+++	+	○	○	++	930	1.011	1.27:1	39	21.7	22.4	1.38	15.9	4.4	+	Diabetes, hemiplegia 7 years ago, pyelitis.
										1190	1.010				40.5					
34	F.	64	175	70	++	+	○	○	○	900	1.010	0.94:1	56	39.9	13.9	3.22	42.4	2.3	?	Diabetes, arteriosclerosis.
										960	1.008				35.6					
35	F.	59	200	110	++	+	++	○	○	260	1.026	0.55:1	25	20.4	30.0	3.6	32.0	....	+	Obesity, diabetes, jaundice, liver, carcinoma.
										470	1.013				53.1					

TABLE I.—(*Continued.*)

Number.	Sex.	Age.	Blood pressure.		Urinalysis.									Phthalein per cent 130 minutes.	McIntosh index of urea concentration.	Fifteen grams urea.			Blood uric acid (fasting).	Rating of cases.	Remarks.
					Albumin.	Casts.		Cells.		Twenty-four-hour urine.						Blood urea nitrogen fasting / 2d hour	Urea concentration 2d hour, per cent (Mac Lean).	Factor (Harrison) U. urea / B. urea			
										7 A.M.–9 P.M.											
										9 P.M.–7 A.M.											
			Systolic.	Diastolic.		Hyaline.	Granular.	Red.	White	Volume cc.	Sp. gr.	Day-night urine volume ratio									
36	F.	56	210	110	++	+	++	O	O	980	1.011	1.02:1		47	22.6	21.0	1.8	24.5	....	+	Diabetes, arteriosclerotic retinitis.
										960	1.012					35.0					
37	F.	59	160	95	+	+	O	O	+	1060	1.008	1.26:1		58	28.3	16.1	1.87	32.8	....	+	Attacks of pyelitis, history of long-standing hypertension.
										840	1.012					26.6					
38	M.	65	186	100	+	Rare	Rare	O	O	420	1.028	0.37:1		37	29.0	30.8	2.9	30.8	5.56	+	Chronic myocarditis, arteriosclerosis.
										1120	1.008					44.0					
													Miscellaneous.								
39	M.	44	120	80	++	+	O	O	O	1420	1.019	1.67:1		64	33.45	25.1	3.28	38.5	....	?	Diabetes, chronic nephritis (?)
										850	1.025					39.8					
40	F.	34	112	88	+	O	O	O	O	1310	1.012	2.94:1		47	40.9	18.9	2.9	32.3	....	O	Chronic tonaillitis, simple goiter.
										445	1.015					41.9					
41	F.	18	95	70	Trace	O	O	O	O	1820	1.004	3. 8:1		58	37.4	11.9	2.3	40.4	3.6	O	Attacks of edema, metabolism minus 20.5 per cent.
										480	1.012					26.6					

42	F.	33	135	85	○	○	○	○	○	1350 290	1.006 1.018	4. 6:1	61	59.7	13.3 26.6	2.4	41.6	3.2	○	Unexplained edema of lower extremities pelvic inflammation.
43	F.	29	110	80	+	○	occa.	○	○	1210 490	1.005 1.008	2.5:1	41	20.55	9.1 27.3	2.11	36.1	....	?	Hepatitis, severe jaundice.
44	M.	15	130	80	++	○	○	○	○	2440 900	1.007 1.013	2. 7:1	57	44.0	14.7 29.4	2.55	40.5	....	○	Diabetes, albuminuria.
45	F.	65	135	70	Spt.	○	○	○	○	1290 305	1.015 1.015	4.23:1	55	25.2	14.0 27.3	2.17*	37.1	....	○	Obesity, diabetes.
46	M.	34	120	80	++	1	○	○	○	1020 500	1.014 1.015	2.04:1	57	43.8	18.1 31.5	3.2	46.9	3.8	○	Marked albuminuria for a period of years.
47	F.	48	145	85	+	○	○	○	○	1020 780	1.007 1.016	1. 3:1	74	35.4	16.8 32.1	3.2	45.41	3.1	○	Diabetes.
48	F.	17	110	80	++	+	+	○	○	500 270	1.020 1.021	1. 8:1	43	35.8	14.0 30.0	3.1	48.6	....	○	Nephritis after secondary syphilis, 8 months' duration.
49	M.	71	...	...	++	+	○	○	○	650 380	1.022 1.021	1. 7:1	51	28.7	7.7 21.7	1.82	39.2	....	+	Arteriosclerosis, diabetes, gangrene of toe.
50	M.	14	110	70	+++	○	○	○	○	870 600	1.017 1.020	1. 3:1	62	36.28	11.9 34.3	2.93	39.92	3.08	?	Post-diphtheritic albuminuria.
51	F.	65	145	85	+	Rare	○	○	○	710 1430	1.015 1.010	0. 5:1	56	21.84	23.8 37.7	1.87	23.18	2.96	+	Diabetes, arteriosclerosis, retinitis.
52	F.	24	110	80	+	○	○	○	○	1700 600	1.007 1.018	2.83:1	56	47.45	16.8 31.5	4.19	62.16	2.60	○	Renal glycosuria, carious teeth.

* Second hour urine volume more than 100 cc.

† Slightest possible trace.

Selection of Cases. Patients having renal lesions with well defined functional impairment were purposely avoided; only 2 such cases were studied (10 and 11). The great majority of the cases had a blood urea nitrogen concentration of 15 to 20 mgm. per 100 cc. Patients having albuminuria with or without casts, arterial hypertension, or edema were chosen as candidates for observation. Many of the patients had diabetes because most of the patients coming to our attention are cases of that nature. None of these cases, however, were employed for this investigation during the time that glycosuria was present; many of them were taking insulin.

Technique of Tests and Normal Standards. *Twenty-four-hour Urinalysis.* On the day that the urine was collected, the patients were kept on their usual diet, including a cup of tea or coffee, and two glasses of water with each meal and one glass of water at 9 P.M. The patients were instructed not to eat or drink anything between meals. Two specimens were collected, the first from 7 A.M. to 9 P.M. and the second from 9 P.M. to 7 A.M. Only the volumes and specific gravities for both day and night urines were estimated and are shown in Table I respectively above and below the cross line. The day-night ratio was determined by dividing the day volume by the night volume and expressing the latter as one. The dividing line between normality and abnormality for this ratio was taken as 2 to 1; this may be less than that allowed by others, but the patients were given a glass of water at 9 P.M. and, further, the majority of the strictly normal cases seemed to put out about one-third of the twenty-four-hour urine volume during the night.

Phthalein Test. The excretion was determined on a 130-minute specimen and was usually done in combination with the urea concentration index (McIntosh). The test was invariably carried out by the same persons and was usually not repeated unless there was reason to question the result. Determinations that were less than 40 per cent, except in the cases of heart failure, were considered definitely abnormal; those between 40 and 50 per cent borderline.

Urea Concentration Index (McIntosh). A 130-minute urine specimen was collected, usually after breakfast. The patient received one glass of water at the beginning of the test. The blood urea was determined in the middle of this period. The index was considered abnormal if it fell below 35.

Blood Urea Nitrogen. This was taken fasting, usually at 9 A.M. Blood urea nitrogen concentrations of over 20 mgm. per 100 cc. were considered abnormal, although in cases of heart failure this is probably not true, and values between 15 and 20 mgm. were held to be of doubtful interpretation.

Urea Concentration Test (MacLean). The patient was allowed neither food nor fluid after the preceding evening meal. Fifteen grams of urea were given by mouth in 100 cc. of water, and the second-hour urine specimen was used, for the specimen providing

it was less than 100 cc.; a few tests had to be repeated in order to accomplish this. Three cases (marked with an asterisk in Table I) are included that had second-hour volumes that considerably exceeded 100 cc., as they could not be conveniently reëxamined. The normal of urea concentration was taken as 2.5 per cent or above in the second hour's urine if the volume was under 100 cc.

Urea Concentration Factor (Modification of Harrison's Method). This was done in conjunction with the urea concentration test. The factor was determined by dividing the urea (mgm. per 100 cc.) of the urine collected during the second hour after the administration of 15 gm. of urea, by the urea (mgm. per 100 cc.) of the blood obtained at the end of the second hour. In Table I the blood urea nitrogen above the line is for fasting while that below the line is for the second hour after giving urea. The minimum urea concentration factor consistent with normal was placed at 40.

The majority of the urinalyses were done personally by the writer. The blood pressure estimations are average readings except in some cases where only one measurement was made. The blood uric acid determinations were made after fasting. The several tests usually occupied less than a week for each patient.

Methods. All the urea determinations both on the blood and urine, were done with the urease-aëration-titration technique, commonly known. All determinations were done in duplicate. The blood uric acid was estimated by the Folin[24] method on a sodium tungstate filtrate.

Clinical Classification of Cases. The classification, as suggested by Christian, was used so as to give as accurate an idea as possible of the types based on clinical study. No attempt was made to analyze the results of the various tests in each class, as it appeared futile.

Analysis of Results. *Division of Cases by Functional Tests.* Three groups were made; a positive, an indeterminate, and a negative. This grouping, of course, is rather arbitrary as the sections blend imperceptibly into one another. The cases comprising the positive group showed a definite disturbance in function in most of the tests, those in the indeterminate group, in at least one of the tests, while the cases in the negative group had either all tests normal or one only that was slightly below normal. Of the 52 cases studied, 22 were considered positive, 15 indeterminate, and 15 negative.

Albumin and Casts in the Urine. Forty-three of the 52 cases had at least a 1+ albumin in the urine while 30 of them had casts. No cases of orthostatic albuminuria were included in the series.

Day-night Urine Volume Ratio. Thirty-four cases, 65 per cent, had a ratio of less than 2 to 1. Only 1 case (Case 1) in the positive group, a young man with definite nephritis and hypertension of some duration, had a ratio of over 2 to 1. Nine cases in the indeter-

minate group and 3 in the negative group had ratios below 2 to 1. In the latter group, Case 19, a nurse with hypertension had a night urine of 700 cc. and a ratio of 0.9 to 1. The other 2 cases in the negative group had ratios just under normal. There appeared to be a general tendency for the specific gravity of the night urine in the positive group to be lower than in the negative group. Seven negative cases and 20 positive cases had a specific gravity of the night urine of less than 1.018.

'Phthalein Test. Twenty-nine patients, 57 per cent, excreted more than 50 per cent of the dye in 130 minutes. Twenty-six per cent of the cases had readings between 40 and 50 per cent and 17 per cent below 40. Seven cases who were judged to belong in the positive group as a result of other tests, had 'phthalein percentages above 50.

The Urea Concentration Index (McIntosh). This index was found below 35 in 32 of the 51 cases (not done on 1 case). All the patients in the positive group, 9 in the indeterminate group, and 3 in the negative group had an index that was below 35. In the negative, there was a variation from 25 to 59.7, the average being 40.

Blood Urea Nitrogen. The fasting blood urea nitrogen was less than 20 mgm. per 100 cc. in 37 of the 52 cases and more than 25 mgm. in 4. It exceeded 20 mgm. in 11 (50 per cent) of the positive and in 1 of the negative cases. In 1 of the indeterminate cases it was 25 mgm.

The Urea Concentration Test (MacLean). The concentration of urea in the urine collected during the second hour after the oral administration of 15 gm. of urea was found to be below 2.5 per cent in 30 cases. Twenty of these were in the positive group, 7 in the indeterminate, and 3 in the negative. The values, however, for these 3 in the negative group were just a shade under the standard, 2.43, 2.4 and 2.3 per cent, respectively. Eighteen of the 30 (below 2.5 per cent) were below 2 per cent, all in the positive group. Two cases (35 and 38) included in the positive group, had percentages of 2.9 and 3.6; both had urea concentration factors that were between 30 and 40. One was a woman of fifty-nine years who had hypertension, diabetes, carcinoma of the liver and marked jaundice; the other was a man aged sixty-five years, who had hypertension and a mild degree of heart failure.

The Urea Concentration Factor (Harrison). The factor was found to be under 40 in all the positive cases, in 9 of the indeterminate cases and in 4 of the negative cases. It was between 30 and 40 in 6 of the negative cases. The average factor in the negative group was 41.5.

The Fasting Blood Uric Acid. This was determined in 27 of the cases studied. The variations in the three groups were not significant. The average for the cases in the negative group was 3.1 mgm. per 100 cc.

Explanation of Table II. This table summarizes the results of the separate tests for each of the three groups of cases, giving the number and percentage in each group that showed positive findings for each test, that is, findings below the normal standard. It will be noted that the tests for the day-night urine volume ratio, specific gravity of the night urine, and the urea concentration index, test, and factor were all positive in at least 90 per cent of the cases in the positive group, whereas the blood urea nitrogen test (over 20 mgm.) was positive in only 50 per cent of the cases of this group. The incidence of positive tests in the negative group is perhaps a better index of the reliability of a given test—the specific gravity of the night urine, blood urea nitrogen (more than 15 mgm.) and the urea concentration factor were considered positive in 40 per cent of the negative cases. A blood urea nitrogen above 20 mgm. was found in only 1 case of the negative group. In the indeterminate group at least one test in each case was definitely abnormal; several of the tests because they were slightly below the minimum standard, had to be classified as positive. That accounts for so many positive results in the indeterminate group.

TABLE II.

Tests.	Positive group. (22 cases).		Indeterminate group (15 cases).		Negative group (15 cases).	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Day-night urine volume ratio, less than 2.1	21	96	9	60	3	20
Night urine volume, 600 cc. or over	17	79	9	60	4	29
Specific gravity of night urine, less than 1.018	20	91	9	60	7	45
'Phthalein excretion, 130 minutes, less than 50 per cent	15	70	4	27	2	13
Blood urea nitrogen, more than 15 mgm.	18	81	5	33	6	40
Blood urea nitrogen, more than 20 mgm.	11	50	4	36	1	8
Urea concentration index (McIntosh)	22	100	9	60	3	20
Urea concentration test (MacLean)	20	90	6	46	3	20
Urea concentration factor (Harrison)	22	100	9	60	6	40

Discussion. The ideal test for renal function would be one that detected and measured impairment of function caused only by renal disease. No such specific test can be hoped for or conceived as possible, because minor grades of functional renal change are often due to extra-renal and temporary causes as well as to renal disease

in the incipient and partly compensated stages. Hence renal function is not necessarily a measure of actual renal damage. Even in true renal disease there must be believed to exist wide variations in function, certainly in the earlier stages. Even our assumed standards of normal function are still subject to dispute by critical observers. It must be clear then that our functional tests cannot be used arbitrarily to define the state of actual renal damage in the large number of cases showing only minor or inconsistent changes in the various functional tests. It appears that the value of these tests is relative, depending upon the degree of departure from normal and the conformity of the several tests and interpreted with reference to the whole clinical picture.

In general, the several tests agreed with each other surprisingly well. There did not appear to be any special reaction for any type of case unless it was in the heart failure group in which blood urea concentrations were proportionately high and 'phthalein readings were relatively low. All observers appear to agree that defective concentration in the day and night urine and excessive volume of night urine are the first manifestations of functional disturbance in chronic nephritis, especially in the type without edema. These changes seem to parallel quite uniformly the ability to concentrate urea except again in the heart failure group where there was, in a number of cases, a large volume of night urine and a normal urea concentration. There appear to be a number of factors, some of them extra-renal, that influence the rate of urine excretion, for example, muscular exercise, atmospheric conditions, rate of blood-flow, nervous excitability, hyperglycemia, and possibly disturbances in the acid-base equilibrium. The concentration of urea does not appear to be affected by these factors to the same extent as the volume and specific gravity of the urine, or, at least, while performing the test standard conditions are more easily brought about, as the patient is under observation for only two hours. Unfortunately about 50 per cent of these patients were studied as out-patients so that uniform conditions did not exist while the twenty-four-hour urine was being collected.

All the tests appeared to give a fairly high percentage of satisfactory results with the exception of the urea tolerance test. The blood urea nitrogen concentration two hours after the administration of urea gave absolutely ambiguous results. In none of the cases did it approach the fasting level; even the positive group did not have uniformly higher values than the other groups.

In the 'phthalein test, a figure of 50 per cent in 130 minutes was required as normal. This is higher than accepted by certain authors and probably some normal people have readings below that figure. Nine of the cases in the positive group had readings below 40 per cent; 2 of these had advanced nephritis and a majority had some degree of heart failure. Therefore, it would appear that this test on the whole is not as delicate as the urea tests.

A fasting blood urea nitrogen of more than 15 mgm. was found in 81 per cent of the positive cases and in 40 per cent of the negative cases. Variations due to diet and other causes occur, but in spite of this as a routine procedure the test appears to work out very well and is helpful in determining whether a patient requires further study. One of its main advantages is that it takes a minimum of time to make the determination and the chances of technical error are small because the specimen is handled by few. A value of over 20 mgm. in the absence of heart failure nearly always means renal damage.

Theoretically, the tests that employ the use of added urea should be best, as a normal urinary constituent is being used, and the kidneys are placed under a strain. However, in these cases, the disturbance of the day-night urine volume ratio and the urea concentration index (McIntosh) gave as high a percentage of positive results in the positive group and as low a percentage of positive results in the negative group as the urea concentration test and factor.

All the tests used appeared to be of some value, and combination of them should give reliable results because any failure by one would be caught by others. As a simple test the urea concentration test (MacLean) appears to have the most advantages and the least disadvantages. We found, however, in comparing the MacLean hypobromite with the urease-aëration technique for the determination of urea, that the former did not give uniformly accurate results. The determination of the factor (Harrison's method) did not give us any added information.

Summary and Conclusions. 1. All the tests of renal function used were satisfactory, but some appear to be more delicate and uniformly reliable than others.

2. Tests that are designed to determine the concentrating power of the kidney should be employed in any routine study.

3. The "urea tests" seem to correspond better with the day-night urine volume ratio and specific gravity than with the 'phthalein test or the blood urea nitrogen. The last two, however, are serviceable as rapid diagnostic measures; other tests may be added when indicated.

4. Based upon the urea concentration test, factor and index, 'phthalein tests of about 50 per cent appear to correspond with normal. Forty per cent as the standard of normal for the 'phthalein test seems too low.

5. The urea concentration index (McIntosh) is a fairly dependable renal functional test.

6. These observations appear to uphold the views of MacLean, in regard to the urea concentration test, that is, any concentration of urea in the urine (second hour) that is below 2 per cent may be regarded as evidence of kidney insufficiency, and if the concentration exceeds 2.5 per cent, renal function is fairly efficient.

7. If it is inconvenient to make blood urea determinations, a satisfactory estimation of renal function may be made by a study of the day-night urine volume ratio and the urea concentration test (MacLean).

8. Any combination of several tests should be dependable for the clinician who is familiar with their interpretation.

9. The determination of the blood uric acid appeared to be without value as a renal function test.

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OBSERVATIONS ON THE ORIGIN OF THE "B" BILE OBTAINED BY LYON'S METHOD OF BILIARY DRAINAGE.*

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In 1919, following an observation of Meltzer[1] on the relaxation of the duodenum in response to the local application of 25 per cent magnesium sulphate solution, Lyon[2] recovered through the duodenal tube in man, first 15 to 20 cc. of golden-yellow bile, followed by 1 to 6 ounces of dark brownish or greenish, at times almost black, bile

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which then became a pale yellow color and could be recovered in any amount. He called them "A," "B" and "C" biles and expressed the belief that they came respectively from the larger bile ducts, gall bladder, and liver with its smaller bile passages. He further stated that the gross, microscopic and bacteriologic examination of these various fractions yields information useful in the diagnosis of gall-tract pathology, especially in the early stages of disease before a diagnosis could be made by any other method.

The origin of the "B" bile has caused much controversy ever since. Since the value of the method for diagnosis depends theoretically on whether gall bladder contents can actually be obtained for examination, this investigation was started to attempt to settle this point. We are not concerned at this time with the various theories dealing with the nerve supply to the gall bladder or the sphincter of Oddi (the existence of which has even been denied) or the mechanism by which the gall bladder empties, but simply whether the so-called "B" bile, or any portion of it, comes from the gall bladder. If it does, study of this bile should be a useful diagnostic measure.

Method. Experimental procedures previously used in dealing with this question consisted for the most part in injecting various dyes into the gall bladder of animals and attempting to recover them from the duodenum. Conflicting results were reported, possibly due to anesthesia, operative injury, shock or these factors combined.[3, 4, 5, 6, 7]

Since the advent of cholecystography,[8] the size of the gall bladder shadow can be determined with a fair degree of accuracy, providing the proper Roentgen ray technique is used. Also, since one of the functions, at least, of the gall bladder is to concentrate its contents,[9] we should expect that if any portion of the bile recovered originated in that organ it would contain seven to ten times or more of the Graham dye (tetraiodophenolphthalein) fourteen hours after its oral administration with the patient fasting, and theoretically, in some cases at least (when it has been promptly absorbed from the gastrointestinal tract) all of it may be expected to reside within the gall bladder. If, then, after the "B" bile is delivered the shadow shrinks markedly in size, and if the "B" bile contains a much higher concentration of iodin than the "A" or "C" biles, and conversely, if no change in size of the gall bladder shadow occurs when we fail to obtain "B" bile, it would appear that it originates in part at least from within the gall bladder.

Procedure. Patients were instructed to take by mouth, two hours after a special evening meal, an average of 60 gr. of tetraiodophenolphthalein (depending on their weight) and to eat nothing until they appeared at the clinic on the following morning fourteen hours later. At this time a gall-bladder Roentgen ray was taken, in some cases before the passage of the duodenal tube, in some while

the tube was in the stomach, and in others after the tip had reached the second portion of the duodenum, depending on the convenience of the Roentgen ray Department. After emptying and washing the stomach, the second portion of the duodenum was intubated and flushed with hot 33⅓ per cent (volumetric) solution of magnesium sulphate or warm olive oil or both, and the bile collected until the end of the clinic period (which lasts three hours) and segregated according to its color. Then another Roentgen ray was taken in as nearly the same position as possible and the size of the shadows compared. If a good "B" fraction was recovered, we should expect to see a marked diminution in the size of the shadow; if only yellow bile appeared, the shadow should remain unchanged.

The various types of bile were then delivered to Dr. Armand Quick (in Dr. J. E. Sweet's laboratory), who analyzed them for iodin content. Also, cultures were taken and the sediment was examined microscopically. (The results of these will be reported later.)

Selection of Patients. Since our object was to compare various degrees of change by Roentgen ray with the character of the bile obtained, patients in whom a Graham test was indicated clinically were used for the most part.

This procedure was carried out completely on 18 patients, 6 men and 12 women. The age of the men varied from twenty-nine to fifty-three, averaging thirty-five years, and of the women from twenty-four to fifty-two, averaging forty-one years. The gall bladders of 5 were definitely mottled by Roentgen ray, 2 showed no shadow, and the outline was suspicious in 2. It was reported as normal in 9.

Results. We have divided our cases for convenience into three groups: (1) In which a good "B" fraction was obtained. By this is meant more than 1 ounce of bile with a definite brownish, dark greenish, or blackish-brown color in the fresh state. (2) In which a very small amount of dark bile or a larger amount of amber colored bile (or doubtful "B" bile) was obtained. (3) In which no dark or "B" bile was recovered.

GROUP I.—A good "B" fraction was recovered in 8 cases. Gall-bladder shadows were present in all before drainage, mottled in 1 case and irregular in outline in another. Magnesium sulphate was instilled alone in 4 cases, with olive oil in 3 and olive oil alone in 1 case. Following the drainage, the shadow disappeared in 1, was markedly reduced in size in 5, and slightly but definitely smaller in 2 cases (the latter 2 being the pathologic gall bladders by Roentgen ray). The average duration of the drainage was one hour and forty-one minutes, varying from thirty minutes to two hours and twenty minutes. For the purpose of computing averages, a "trace" is counted as 0.005 per cent and a "faint trace," 0.001 per cent. The iodin content of the "A" biles averaged 0.002 per cent; of the "B"

biles 0.096 per cent; of the "C" biles 0.0089 per cent. The "B" biles, therefore, contained an average of forty-eight times as much iodin as the "A" and 10.8 times as much as the "C" fractions. In 1 case, neither the "A" nor "C" biles contained any iodin and the "B" fraction had 0.133 per cent. In the 1 case in which the shadow disappeared, magnesium sulphate alone was used.

TABLE I.—CASES WITH GOOD "B" FRACTION.

Clinic No.	Sex.	Age, yrs.	Reduction in size of shadow.	Iodin content, per cent.			Duration of drainage.
				A.	B.	C.	
98056 . .	F.	52	Marked	...	...	...	1 hr. 55 min.
89452 . .	M.	29	Disappeared	...	...	...	2 hrs.
99137 . .	F.	49	Marked	...	...	...	1 hr. 50 min.
95515 . .	F.	37	Marked	Trace	0.100	0.0070	2 hrs.
90128 . .	F.	31	Marked	0.005	0.076	0.0050	2 hrs. 20 min.
92065 . .	M.	30	Marked	None	0.120	0.0075	55 min.
A1884 . .	M.	29	Slight*	None	0.050	0.0250	2 hrs.
93586 . .	F.	44	Slight†	None	0.133	None	30 min.

* Mottled. † Irregular.

The iodin method used for the first 3 cases was found by Dr. Quick to be inaccurate and the results discarded, although they parallel the other figures. In patient 95515 the drainage was repeated after giving atropin. Amber-colored "B" bile was obtained, the shadow decreased only moderately in size, and the iodin content of the darkest bile was 0.03 per cent instead of 0.1 per cent.

GROUP II.—In 5 patients either only a few cubic centimeters of dark bile or a larger amount of amber-colored bile was obtained. The Roentgen ray shadow was reported as mottled in 2 and normal in 3. Magnesium sulphate alone was used to stimulate bile flow. Following drainage a slight reduction in size occurred in 4 cases and it appeared unchanged in 1, even after a subsequent high-fat meal. The iodin determination was discarded in 1 case for the reason stated. In the others the "A" fraction averaged 0.005 per cent of iodin, "B" 0.041 per cent, "C" 0.014 per cent, the "B" bile containing eight times as much iodin as the "A" and 2.9 times as much as the "C." In patient 92565, a young woman suffering from attacks of migrain with vomiting of bile, the "C" fraction contained considerable bile-stained mucus with an iodin content of 0.15 per cent, the supernatant fluid having 0.025 per cent iodin. The "B" bile contained less iodin and the "C" more than in Group I.

GROUP III.—Five patients failed to show a definite darkening of the bile following the instillation of magnesium sulphate and olive oil. Of these 2 showed no gall-bladder shadow, 1 a mottled shadow, 1 a semilunar-shaped, and 1 an apparently normal gall-

bladder shadow. In no case did the shadow decrease in size following drainage. The iodin content of these biles was about the same before and after stimulation, only traces being found or none at all.

TABLE II.—CASES WITH SMALL OR DOUBTFUL "B" FRACTIONS.

Clinic No.	Sex.	Age, yrs.	Reduction in size of shadow.	Iodin, per cent.			Duration of drainage.
				A.	B.	C.	
93589	M.	38	Slight*	...	...	...	1 hr.
98273 . .	M.	30	Slight	0.005	0.075	0.015	1 hr., 10 min.
92565 . .	F.	29	Slight	Trace	0.015	0.025	1 hr.
90718 . .	F.	24	Slight*	Ft. tr.	0.015	Ft. tr.	2 hrs.
A2861 . .	F.	50	None	0.010	0.060	0.010	50 min.

* Mottled.

TABLE III.

Clinic No.	Sex.	Age, yrs.	Roentgen ray.	Iodin, per cent.		Duration of drainage.
				A.	C.	
99237 . .	M.	53	No shadow	Ft. tr.	0.007	1 hr., 45 min.
24553 . .	F.	43	No change	Ft. tr.	Ft. tr.	2 hr., 50 min.
97076 . .	F.	47	No shadow	...	...	2 hrs.
29623 . .	F.	35	Semilunar; no change	....	....	2 hrs.
98986 . .	F.	46	Mottled; no change	None	Trace	2 hrs.

Discussion of Results. It would appear, from these findings, that the delivery of one or more ounces of a brownish, greenish, or black bile through the duodenal tube, following the introduction of 33⅓ per cent magnesium sulphate solution or of olive oil into the duodenum, is accompanied by a marked decrease in the size of the gall-bladder shadow, except in two pathologic gall bladders where the shrinkage was slight but definite. That when no dark bile is obtained (even though large amounts of yellow bile are recovered) the shadow, if present, does not decrease in size, and when less than 1 ounce of dark bile or larger quantities of an amber-colored fluid are recovered, the gall-bladder shadow decreases slightly in size or (in one case) not at all. It may be further stated that by far the greatest concentration of the tetraiodophenolphthalein given fourteen hours previously is contained in this dark bile. The color of the bile is not dependent on its rate of flow[10] as large amounts of golden or pale yellow bile-stained fluid may be recovered in much shorter time than an equal amount of dark bile. Although usually it becomes dark a few minutes after the magnesium sulphate is introduced, in some cases as much as 150 cc. of light bile is obtained

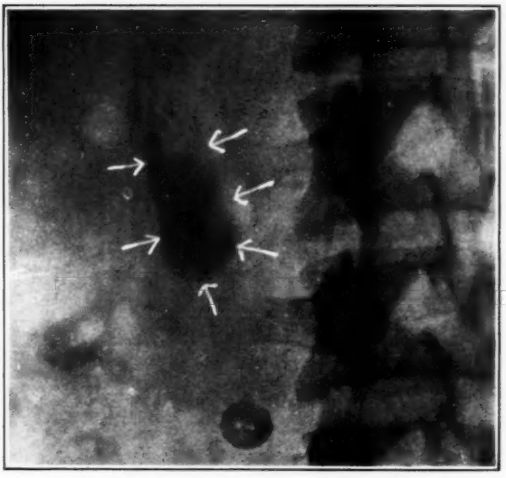

FIG. 1A.—Case No. 89425 before drainage.

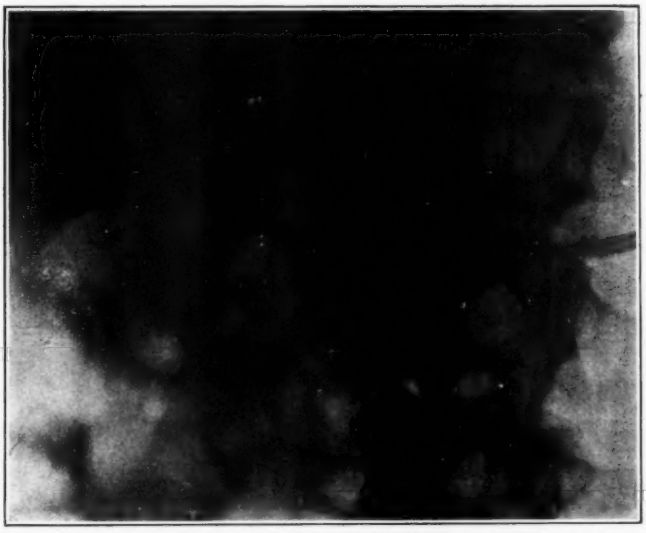

FIG. 1B.—Same, two hours after the instillation through the tube of 33⅓ per cent magnesium sulphate, followed by the recovery of 80 cc. of blackish-brown bile. The shadow has disappeared.

FIG. 2A.—Case No. 92065 before drainage.

FIG. 2B.—Same, after 75 cc. of yellowish-brown bile was recovered, fifty-five minutes after the instillation through the tube of 33⅓ per cent magnesium sulphate solution.

FIG. 3A.—Case No. 99137 before drainage. Tube is at the pylorus. This patient has a marked scoliosis.

FIG. 3B.—Same, one hour fifty-five minutes after the instillation of olive oil; 80 cc. of brownish bile was obtained.

FIG. 4A.—Case No. 95515 before drainage.

FIG. 4B.—Same, two hours later; 33⅓ per cent magnesium sulphate was instilled through the tube and 25 cc. of dark amber bile recovered.

FIG. 5A.—Case No. 98273 before drainage.

FIG. 5B.—Same one hour 10 minutes after the instillation of magnesium sulphate solution, with recovery of only 5 cc. of brown bile and 60 cc. of yellow bile. Slight if any change in the size of the shadow.

and then it suddenly becomes darker and as abruptly light again. This may occur two or three times without further stimulation.[11] It was delivered in one fraction in 5 cases, in two layers once and as three distinct fractions in 2 cases. In 1 case, which was drained on the Roentgen ray table, the sound of the machine was followed on three occasions by the bile promptly turning a light color and after a few minutes becoming dark again. It has been frequently stated by Whitaker[13] and others that the change in size of the gall bladder shadow is very slight following the local application of magnesium sulphate to the duodenum. These results indicate that the degree of the shrinkage is proportional to the amount of dark bile recovered and is frequently very marked.

In interpreting the significance of the iodin content of the "B" bile it must be borne in mind that we are dealing with bile diluted by water used in the gastric lavage, a certain amount of magnesium sulphate, gastric, duodenal and pancreatic secretions as well as the bile coming down from the liver. According to Graham and his coworkers,[12] an actual concentration in the gall bladders of animals of as low as 0.45 per cent of bromin will cast a dense shadow by Roentgen ray. Since the atomic weight of iodin is 127 and of bromine only 80, we should expect a much lower concentration of iodin to cast a good shadow. In one human gall bladder (pathologic) removed at operation, the patient having been given 60 gr. of the dye by mouth on the previous day, the concentration of iodin was found to be 0.76 per cent. It seems reasonable to suppose, therefore, when we allow for dilution in transit, that a bile containing about 0.1 per cent iodin probably represents gall-bladder bile in part.

In the second group of cases, the decrease in iodin concentration of the "B" fraction is accompanied by an increase in the "C" biles, suggesting a slower gall-bladder response with consequently greater admixture from above, so that the "C" fraction is still receiving traces of gall-bladder bile. This is further borne out by the fact that in our third group, where no "B" bile is present, the iodin concentration of the "C" fraction again becomes very low.

Atropin (in one case) seemed to inhibit to some extent the changes described.[13]

If the change in size of the shadow were due entirely to absorption[14, 15] of bile through the gall-bladder wall, we should expect to find an occasional case where this shrinkage is not accompanied by the delivery of a dark bile. This has not occurred in this series. Also it seems improbable that absorption could be so rapid as to cause a marked change in size in fifty-five minutes or a detectable change in thirty minutes, and it could not explain the differences in iodin content of the various fractions.

Studies are being made on the iodin content of biles from cholecystectomized patients.

Summary. 1. The recovery through a duodenal tube of 1 ounce or more of brownish, dark greenish or black bile following the instillation of magnesium sulphate or olive oil is accompanied by a considerable decrease in the size of the gall-bladder shadow by Roentgen ray, or (in one case) its disappearance.

2. The dark bile so obtained contains an average of 48 times as much iodin as the bile that precedes it and 10.8 times as much as the bile that follows it, and may be the only fraction containing any iodin (fourteen hours after the oral administration of sodium tetraiodophenolphthalein).

3. When no dark bile is recovered, even though large amounts of yellow bile appears, the gall-bladder shadow is either absent or does not decrease in size.

4. When a smaller amount of dark bile or a larger amount of amber-colored bile is secured, the gall-bladder shadow decreases slightly in size or (in one case) not at all.

Conclusion. The above results seem to indicate that samples of bile from the gall bladder can be recovered through the duodenal tube for microscopic and bacteriologic examination.

NOTE.—I am indebted to Dr. Lyon for the opportunity of working in his laboratory in order to learn his technique in preparation for this problem, to Dr. John R. Carty for the Roentgen ray plates, to Dr. Armand Quick for the iodin determinations and to Drs. H. H. Fellows and J. E. Sweet for many helpful suggestions.

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ICTERUS NEONATORUM GRAVIS.

Report of a Case which Recovered with Sequelæ Pointing to an Involvement of the Central Nervous System.

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Icterus neonatorum gravis is an almost uniformly fatal disease; occasionally, however, recovery does occur. This case is reported because of cerebral symptoms which made their appearance six months after recovery. A search of the literature reveals only 11 cases thus far reported (Guthrie,[1] Spiller,[2] Hart,[3] Pitfield,[4] Arkwright[5] and Hoffman and Hausmann[6]) which recovered and subsequently presented evidences of pathologic changes in the central nervous system.

Case Report. D. G., was born in the United Israel Zion Hospital, Brooklyn, N. Y., on January 16, 1925, weighing 7 pounds. This was the mother's third pregnancy and delivery, normal and spontaneous in all respects, the duration of labor being six and one-half hours.

The two previous pregnancies and deliveries were also normal and spontaneous. The first child, however, died on the fifth day after birth with evidences of a severe icterus. The second died on the eleventh day with similar manifestations. In the first child, marked jaundice was observed twenty-four hours after birth, which persisted until death. On the third day, the infant had a convulsion and bleeding occurred from the umbilicus. Similarly, the second

infant exhibited a deep icterus after twenty-four hours, convulsions developing forty-eight and seventy-two hours after birth, but no evidence of hemorrhages occurred at any time. In neither case was a necropsy performed. The patient whose case is reported here also developed icterus twenty-four hours after birth, which, according to the mother's statement, was just as marked as in the other two infants.

On the day after delivery, examination of the child revealed the following: The infant was fairly well nourished and had a lusty cry, good muscle tone, but poor turgor. The weight was 6 pounds, 8 ounces, showing a loss of 8 ounces in two days; the anterior fontanelle was open and depressed, and measured 4 by 5 cm. The skin was dry and deeply jaundiced; the eyes, aside from the deep icteric tinge of the sclera, were negative. The cervical, axillary and inguinal lymph glands were not enlarged; the throat was clear; heart and lungs were negative. The abdomen was moderately distended but the liver and spleen were not palpable; the genitalia, extremities and reflexes were negative. Temperature, pulse and respiration were normal. The red blood count was 4,800,000, hemoglobin 78 per cent (Sahli); the white blood count was 14,200, of which 72 per cent were polymorphonuclear leukocytes and 28 per cent lymphocytes; the bleeding time was six minutes, and the coagulation time four minutes, normal figures which corresponded to those found at birth. Examination of the urine revealed no leucin or tyrosin crystals. Bile pigments were present; urobilinogen was absent; a few biliary casts were found. The stools were brown, and were positive for bile pigments. The Wassermann reaction of the mother taken during pregnancy and from the cord blood was negative.

These findings together with the history justified a diagnosis of icterus neonatorum gravis; congenital atresia of the bile ducts could be ruled out because of the presence of bile pigments in the stools. The child refused the breast and was, therefore, given expressed mother's milk with equal parts of water. When breast feeding was resumed, complementary feedings of cow's milk and equal parts of water were given temporarily, and were later discontinued. The infant was discharged from the hospital on February 1, 1925, weighing 6 pounds, 15 ounces; at this time the icterus was still marked. The infant was taking the breast well.

The jaundice persisted up to five weeks of age. The child constantly maintained a normal weight curve for its age. Repeated tests of the bleeding and coagulation times were normal.

On August 7, 1925, when six months of age, the child was not able to support its head. The weight was 15 pounds and 12 ounces. There was definite spasticity of the adductor muscles of the thigh and static function was absent. Although the infant smiled and followed an object, it made no attempt to grasp it. At one year of age, when held under the arms, the child could stand, but only on

its toes, with the legs crossed. It was still unable to hold up its head. When one and a half years old the infant was not able to sit or stand, walk or talk. Examination on May 13, 1927, revealed the following: The child had a definite idiotic appearance, did not talk beyond saying "yes" and "no" distinctly, and "mama" and "water" which it articulated indistinctly; it was now able to support its head, but there was still a tendency to unsteadiness. It was able to stand on its toes, but could walk only when supported under the arms; the gait was spastic and unsteady. There was a bilateral spontaneous Babinski and an absence of the cremasteric and abdominal reflexes. The child made an attempt to grasp objects but showed evidences of lack of coördination of the muscles of the upper extremities.

Comment. Icterus gravis is characterized by the fact that the jaundice appears early, at times, even a few hours after birth; in exceptional cases, however, it may not make its appearance until the infant is several weeks old. The jaundice increases rapidly and soon becomes intense; anorexia is marked, and severe nervous manifestations, such as convulsions and coma, rapidly make their appearance. The urine contains bile pigments and the stool is not acholic. Death usually occurs from the third to the tenth day. It may be confused with icterus neonatorum, syphilis, sepsis and congenital atresia of the bile ducts. The following table from Meyer[7] will be of aid in the differential diagnosis:

	Bile pigment reaction in urine.	Bile pigment in stool.	Time of appearance of jaundice.	Fever.	General condition.
Icterus neonatorum	Absent	Present	2 to 10 days	Absent	Good.
Icterus gravis . .	Present	Present	1st day; later in the exceptional case	Absent except just before death	Very poor.
Icterus accompanying sepsis . .	Present	Present	Indefinite	Present	Very poor.
Syphilitic icterus .	Present	May or may not be present*	Indefinite, usually after the third day of life	May or may not be present	Poor.
Congenital atresia of bile ducts . .	Present	Absent	In course of first few days or weeks of life	Absent	Good at first; becomes poor as infant grows older.

* Bile pigments are absent in the stool if a gumma is present and compresses the bile duct.

Little is known of the pathogenesis of icterus gravis. Several infants in the same family may exhibit it, but not always in succession. The ordinary icterus neonatorum may occur in other infants of the same family, and not every case of icterus gravis is necessarily fatal. The disease is less likely to occur in the first and second child than later, although the first and second infants of this mother died of this disease. Several causes have been suggested. Schminke[8] states that the pathogenesis is still an open question and quotes

Lagrèze[9] as believing it due to a congenital intoxication of the fetus through toxic maternal metabolic products. Knöpfelmacher[10] believes icterus gravis should be considered as a type of septic jaundice and suggests that its repeated appearance in one family is merely incidental. Thorling,[11] Beneke,[12] Esch,[13] and Pfaltzer[14] also take this viewpoint. Rolleston[15] is of the opinion that maternal toxemia during pregnancy is an important factor in the pathogenesis of this condition. Pfannenstiel[16] and Yllpö[17] believe that it is due to a functional insufficiency of the liver tissues; they affirm that the insufficiency of the liver cells permits the entrance of bile into the blood and that death occurs from the resulting cholemia. Syphilis has also been advanced as a causative factor. It is not likely that sepsis or maternal toxemia were factors in the case here reported, because at no time, before, during, or after delivery, did the mother complain of any untoward symptoms; there was no elevation of temperature at any time. In view of the previous history, the mother was carefully observed during her pregnancy. Repeated Wassermann examinations of the blood from the father and mother were negative, thus ruling out syphilis as a possible factor.

Hoffman and Hausmann[6] believe the condition to be due to a toxin which is apparently harmless to the mother, but detrimental to her offspring. They believe that these infants are born with a tendency to icterus, and point to the fact that the jaundice appears at birth or shortly after. According to them, a hemolyzing toxin is produced causing an increased destruction of red blood cells. They report a series of 5 cases which recovered and which later manifested symptoms pointing to an involvement of the central nervous system. Two cases occurred in one family. The nervous symptoms observed were opisthotonos, trismus, spasticity of the extremities, epileptiform attacks, and spasms of the muscles of deglutition. Imbecility was present in the children that lived longer than three months. The cases reported by Spiller,[2] Guthrie,[1] Hart,[3] Pitfield,[4] and Arkwright[5] also presented motor disturbances of various types and intelligence defects. In 2 of Hoffman's[6] cases that came to necropsy, necrosis of the ganglion cells of the basal nuclei and round cell perivascular infiltration were found. In necropsies performed on newborn infants dying of this disease, Schmorl,[18] Esch,[19] Beneke,[20] Hart,[21] Yllpö[22] and Pfannenstiel[16] found icteric pigmentation and extensive necrosis of the ganglion cells of the basal nuclei, of the medulla, of the olivary bodies and of the gray matter of the anterior and posterior horns of the cord. Esch[19] is of the opinion that the bulbar symptoms (inability to swallow, disturbances of respiration) which are encountered at times are due to the changes in the nuclei of the cranial nerves. Icteric pigmentation is not constant, however. Pfannenstiel[16] observed it in 2 of 6 cases, Yllpö[22] in 1 of 2 cases. Klemperer[23] reports the results of 2 necropsies in cases which clinically belong in this group. The liver in both cases showed a

diffuse necrosis and destruction of cells, most conspicuous in, but not limited to, the central areas of the lobule. Klemperer,[23] in his report, does not state the results of examination of the brain. In none of the cases were cerebral hemorrhage or lesions pointing to cerebral injury found.

Hoffman and Hausmann[6] believe that there is a definite relationship between the severe liver disturbance and the pigmentation and necrosis of the ganglion cells in the basal nuclei which occur in this condition. It is their opinion that the changes are not due to an excess of bile pigments in the blood, because: (1) The lesions of the central nervous system are not encountered in every case of icterus gravis; they occur only in the cases where definite necrosis of the liver cells are met with. (2) Cerebral symptoms are never observed in the severe cholemia which always accompanies congenital atresia of the bile ducts. They advance the theory that the necroses of the ganglion cells may be due to lipolytic substances produced by the destruction of liver tissue and which have an injurious effect on the brain tissue. The lack of resistance of the brain tissue of the newborn would make it seem plausible that a toxin will produce a greater destructive effect here than elsewhere in the body.

To support their view they point to the cerebral symptoms as delirium, convulsions, trèmors and the like, which occur in acute yellow atrophy, a condition in which extensive liver necrosis occurs; also to changes which occur in the brain of infants suffering from septic icterus when septic hepatitis is present simultaneously. Cerebral necrosis does not occur unless hepatitis is present. Spiller,[2] too, believes that the severe jaundice has an etiologic relation to the spastic cerebral diplegia which is found in the cases that recover. Schütte[24] found extensive lesions in the liver in a case of progressive disease of the central nervous system which on necropsy manifested extensive destruction of nerve fibers and nerve cells and overgrowth of neuroglia. In the infant whose case is here reported, although it is impossible to exclude absolutely cerebral hemorrhage as a possible factor in the production of the nervous symptoms present, it is our belief that the nervous symptoms are due to a cerebral necrosis as a direct result of liver changes, as manifested by a severe icterus. Against cerebral hemorrhage as a possible cause, we point to the fact that the delivery was spontaneous, that the infant was full term, that hemorrhages were not present elsewhere in the body, and that the bleeding time and coagulation time were normal. In addition, the other two infants born of this mother presented cerebral symptoms on the second and third days of their lives, despite the fact that the deliveries were normal and spontaneous. To support our view, we point to the fact that cerebral hemorrhage was not found at necropsy in any of the cases of icterus gravis with cerebral symptoms reported by other observers, but that cerebral necrosis and perivascular round-cell infiltration were the lesions present.

From our observation of the case reported and in view of the pathologic changes in the central nervous system reported by the observers quoted above, we feel justified in stating that icterus neonatorum gravis must be considered as a causative factor in cerebral diplegia. Only too often is cerebral diplegia falsely attributed to cerebral hemorrhage at birth.

Ford,[25] too, states that true congenital cerebral diplegia is apparently unrelated to birth injury or meningeal hemorrhage. He believes that the greater percentage of infantile spastic palsies is the result of various pathologic processes of intrauterine origin and he quotes Batten as stating that cerebral diplegia is the result of four different pathologic conditions: (1) Atrophic sclerosis; (2) arrested development of the brain; (3) intrauterine occlusion of the cerebral vessels; (4) various types of meningitis. As a fifth possible cause we include icterus neonatorum gravis.

Treatment. Treatment is practically of no avail. Prophylactic treatment, however, does offer some encouragement. Pitfield[4] recommends large doses of calcium chlorid and a vegetable diet during pregnancy. Rolleston[15] administers urotropin and sodium salicylate during the entire period of gestation to prevent bile stasis and for intestinal disinfection. Breast milk is the best method of feeding in these cases. Hoffman and Hausmann[6] recommend skimmed breast milk in small amounts, not from the mother, but rather from a wet nurse, because of the possibility of the presence of toxins in the mother's milk. Whether toxins are excreted in the mother's milk, however, is questionable. The infant, whose case is reported here, was fed milk expressed from the mother's breast, and apparently showed no ill effects from it.

Spiller[2] advises transfusions. Pitfield[4] has also found injection of whole blood of value. Klemperer[23] advocates the intravenous injection of glucose as of possible value. It has also been suggested to employ injections of glucose into the mother during pregnancy.

Summary. 1. A case of familial icterus neonatorum gravis with recovery is reported; the first two infants of the same mother having suffered from this disease with fatal termination.

2. Symptoms pointing to an involvement of the central nervous system as evidenced by spastic diplegia and idiocy developed subsequently.

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TENDERNESS OF THE STERNUM IN LEUKEMIA.

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Most textbooks and systems of medicine in discussing myelogenous leukemia mention tenderness of the bones as a frequent symptom. Some authors make special note of sternal tenderness. No one, however, appears to have described the peculiar features of the sternal tenderness, and many authors fail to emphasize how definite and striking a phenomenon this sign may be in a large proportion of cases of myelogenous leukemia, in which otherwise the enlarged spleen and the characteristic blood picture may be almost the only objective findings.

Tenderness of other bones, such as the ribs and tibiæ, is rare in myelogenous leukemia in comparison with the frequency of sternal tenderness. Other diseases, such as mediastinitis, mediastinal tumor or aneurysm may be accompanied by sternal tenderness; but in these diseases the location of the tenderness and the concomitant signs are likely to be quite at variance with the typical tenderness of the sternum as seen in myelogenous leukemia. An occasional case of lymphatic leukemia, pseudoleukemia, Hodgkin's disease or lymphosarcoma may have sternal tenderness similar to that seen in myelogenous leukemia. As for the frequency of this sign in other diseases accompanied by splenomegaly, no information is at hand.

The first description of sternal tenderness in leukemia, according to Muir, was by Mosler in 1876. However, in Mosler's case there were gross changes in the sternum. It was bulging and was softened

at one spot; and Mosler states that he made the diagnosis of leukemia "during life" in this case by a study of bone marrow aspirated from the softened area. None of the cases in this series had any changes in the structure of the sternum that could be seen or felt during life.

The typical features of sternal tenderness in myelogenous leukemia are as follows: The sign is seldom present over the entire sternum, being almost always limited to the gladiolus. The manubrium has not been found tender in any case in this series. The tender area may be so small that it may be completely missed, and in such instances it is almost invariably found at one definite point. This point is in the midline opposite the fifth costal cartilage. The tender area may be no larger than the tip of one's finger, and several cases have been seen in which moderate pressure at this point, and no other, will cause severe pain. Furthermore, the extent of the tender area, and the degree of tenderness in a given case are often roughly proportionate to the degree of illness of the patient. Thus, in a patient who is acutely ill, the tenderness may be found over most of the gladiolus, and it may be so marked that slight pressure will cause excruciating pain, lasting for several moments after the pressure has been released.

After treatment of the spleen with radium (without any radiation over the sternum), one will often find, along with the improvement in the general condition and in the blood picture and the shrinkage of the spleen, that the degree of tenderness has become much less, and the width of the tender area much smaller, so that it might be overlooked if one did not locate the definite point which was described above. With further remission in the disease the tenderness may completely disappear. Finally, with an exacerbation of the disease the tenderness may reappear, first at the small point in the midline opposite the fifth rib cartilage; and with further decline in the patient's condition the area may again become wider.

Occasionally, the patient himself has discovered the sternal tenderness. In 1 case that discovery was the first intimation of illness. Sometimes pain, not related to pressure, has been felt in the region of the sternum, less frequently in other bony regions.

In the past seven years 40 cases of myelogenous leukemia have been treated at the Memorial Hospital. In many of the earlier cases sternal tenderness was not looked for systematically; or if it was looked for was perhaps missed, because it is only since about 1922 that the peculiar features of this sign, as described above, have been known. Its presence or absence has been recorded in 18 cases; and of these it was found present in some degree, or at some time in the course of the disease in 17, or 94.4 per cent. This percentage is probably too high, as some negative findings may not have been recorded. However, it is probable that some positive

findings, too, may not have been recorded, as bone tenderness is usually considered a minor symptom in leukemia. It is believed that a safe estimate would be that at least 75 per cent of cases of myelogenous leukemia will show this sign at some time during their course. Tibial tenderness was found in only 2 of the 18 cases, and in both of these it was of slight degree, while the sternal tenderness was pronounced.

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GAS GANGRENE IN CIVIL PRACTICE.

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In reviewing the literature of gas gangrene, one is impressed with the relative paucity of discussions of cases occurring in civil practice. One is, therefore, led to believe that this disease is rare. The purpose of this discussion is to present the results of a study of 85 cases from the records of Bellevue Hospital, to call attention once again to the value of debridement and to advance arguments for a fair trial of serotherapy.

Maisonneuve[1] first described gas bacillus infection in 1853. Salleron,[2] a year later, reviewed 65 case histories collecting his material from a study of casualties occurring during the Crimean War. This, it must be recalled, preceded Pasteur's epochal announcement of the relation of bacteria to disease. After infecting animals with putrid flesh, Pasteur discovered in 1876 the organism now referred to as the Vibrion septique. He did not, however, obtain a pure culture. Five years later, 1881, more detailed study of the same bacterium was undertaken by Koch and Gaffky[3] who gave it the name of Bacillus edematis maligni. A year later, Molier and Ponget, for the first time, used the term of gaseous gangrene.

Thus far, the Vibrion septique or the Bacillus edematis maligni was the only organism associated with gas gangrene. It was not until 1892, ten years later, that Welch and Nutall[4] described minutely their bacillus isolated from the bloodvessels of a patient suffering from aortic aneurysm. Working in the autopsy room of

the John Hopkins University Medical College, they noticed that the vessels were distended with gas bubbles. This observation was followed by the discovery of the gas bacillus in the barrel of their hypodermic syringe. A year later, 1893, Fraenkel,[5] working independently, isolated the same organism, called by Welch the Bacillus aërogenes capsulatus, known also as the Bacillus welchii, and referred to by the French as the Bacillus perfringens.

The succeeding two decades added very little. With the outbreak of the World War in 1914, however, with its thousands of cases infected by gas bacilli, so plentiful in the oft-manured soil of France and Belgium, the question became an outstanding medical problem. In the British army alone, during the early years of the war, from 10 to 12 per cent of all wounds became infected with gas bacilli, the mortality varying from 9 to 50 per cent.[6] The interest of numerous investigators was aroused. Much of the work carried on at that time was by Wallace of Great Britain, de Lavergne, Weinberg and Leclainche of France. Most of the research in this country was undertaken by Taylor, Bull and Pritchett.

With the signing of the armistice, interest began to wane. There were, of course, occasional reports of a few cases occurring in civil practice. Within the past five years Dayton, Hardy, Pilcher, Gemmill, Goodman, Baugher, Fortuine and Vickers, Tenopyr, Ochsner and Schmidt and others have added case reports to the literature of gas gangrene.

Bacteriology. The Bacillus welchii, Vibrion septique, and Bacillus edemaciens are the predominating organisms. Less frequently, and often in association with the above, one finds Bacillus hemolyticus, Bacillus fallax, Bacillus egens, the "Reading bacillus," and Bacillus bellonensis. Park and Williams[7] state that "in the rare infections in civil practice the Bacillus welchii is sometimes met with in pure culture."

Practically no organism can be demonstrated by culture until at least four hours or, by direct smear, until at least six hours after the infection. Bull and Pritchett,[8] and Weinberg[9] have shown that the Bacillus welchii produces an exotoxin which, in their opinion, is a complex of an hemolysin and another poisonous body. It is their contention that the exotoxin may be controlled by an antitoxin.

Essentially, infection by the above organisms depends upon a lack of oxygen in devitalized tissue. Thus, direct trauma, shock with its resultant diminution of blood supply to the part, and the symbiosis of aërobic with anaërobic bacilli play an all-important rôle in the production of gas gangrene.

Incidence and Mortality. At the end of the war from 1.5 to 3 per cent[6] of all wounds were infected by gas bacilli. With earlier and better care the English were able to reduce their morbidity rate

from 11 per cent in the first years of the war to 1 per cent in 1918.[10] Keen,[11] however, until the same year, had seen but 1 case in civil practice; while Pickard of Kansas City[12] encountered but 3 cases over a period of fifteen years of railroad surgery. Fortuine and Vickers[6] report only 3 cases in 2814 admissions to the Mary McClellan Hospital of Cambridge. D. Guthrie,[13] in a statistical study of the records of Bellevue Hospital from 1909 to 1911, found 1 case in every 644 admissions (0.0005 per cent).

The series herewith presented covers a period of fifteen years, 1911 to 1926. During this period, there were 618,105 admissions to Bellevue Hospital of which there are recorded 85 cases of gas bacillus infection, an incidence of 1 in 7310 or 0.0001 per cent.

To comment upon this striking difference in incidence of gas-bacillus infection in war and civil practice, one need but call attention to the highly fertilized fields of France and Belgium as compared with the streets of New York City.

As previously stated, mortality statistics varied from 9 to 50 per cent, depending upon the period that elapsed from the time of injury to that of treatment. A. Chalier[14] reports the mortality from gas gangrene as 24 per cent in the circumscribed or gaseous phlegmonous variety, and 67 per cent in the diffuse form. Furthermore, the location of the wound decidedly influenced the mortality rate. In Vincent's series[10] war injuries of the head, neck, chest, thorax, abdomen and genital organs were subject to a mortality of 54 per cent, those of the lower limbs, 36 per cent; while those of the upper limbs, only 20 per cent.

In the Bellevue series of 85 cases there were 39 deaths, a mortality of 45.9 per cent. In this group, the deaths in a series of 40 cases of injuries limited to the extremities were 20, or 50 per cent. Tables I and II are graphic reviews of these 85 cases. The extremities were involved in 61 instances (71 per cent), of these, 26 cases were compound fractures (30 per cent). Twenty-three were of the lower and 2 of the upper extremities and 1 of the pelvis (see Table I). One case developed gas gangrene following a laceration of the scalp. This is of interest in view of Bowlby's statement[15] that he has never seen a case of gas gangrene of the head. This type of infection is sometimes seen in diabetics and occurred in 4 instances of the series herewith reported. Inasmuch as glycosuria occasionally develops in the course of gas gangrene,[16] as was instanced in Case I, one must be careful not to diagnose diabetes mellitus from the urine examination alone.

TABLE I.—ANALYSIS OF TWENTY-SIX COMPOUND FRACTURES.

Lower extremity	23	Upper extremity	2
Tibia	15	Humerus	1
Femur	5	Radius	1
Foot and ankle	3	Pelvis	1

TABLE II.—REVIEW OF EIGHTY-FIVE CASES ASSOCIATED WITH GAS GANGRENE.

Compound fractures	26
Lacerations	17
Extreme multiple injuries	6
Avulsions	4
Diabetes mellitus	4
Gangrene of extremity	4
Lobar pneumonia	2
Acute alcohol poisoning	2
Rectal abscess	2

Solitary Cases.

Gunshot wound of lung	Sarcoma of kidney
Gunshot wound of liver	Carcinoma of intestine
Gunshot wound of abdomen	Varicose veins
Hydrocele of tunica vaginalis	Chronic morphinism
Septicemia	Erysipelas
Bronchial asthma	Abscess of male perineum
Rupture of the urethra	Phlebitis
Acquired deformity of bladder	Rupture of duodenum
Gangrene of scrotum	Crushing injury of an extremity

Incubation Period. Virulent infections may set in within several hours after injury. Late infections, according to Zindel,[17] may be equally malignant. As a rule the first signs of gas gangrene appear between two to five days after the injury is sustained. The average incubation period in the Bellevue series was three days, although in 1 case this was shortened to one day and in another delayed for eleven days.

Sex and Age. The vast majority occurred in males. The greatest incidence was in the sixth decade, as shown by chart. No case was found under the age of five years.

Theories.[8] Various theories as to the cause of gas gangrene have been proposed.

1. Fraenkel believed that the symptoms were due to the absorbtion of decomposition products from the affected tissues.

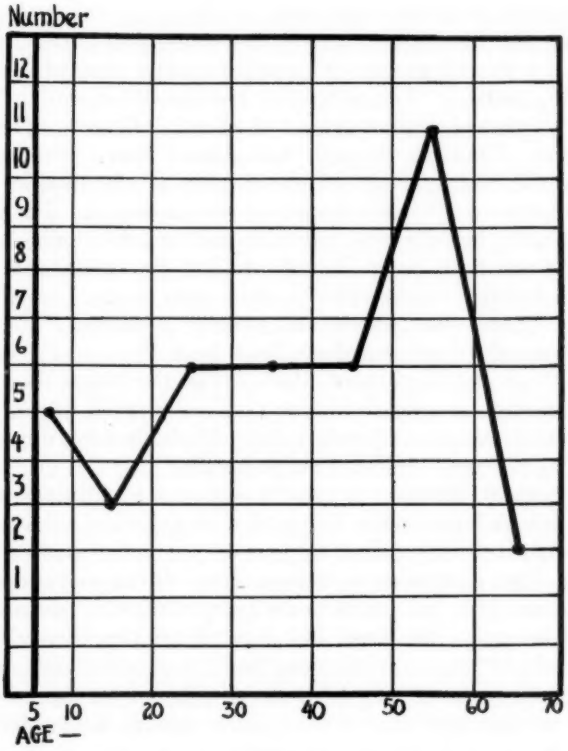
2. Metchnikoff, Korentschewsky, and others attributed the constitutional symptoms to "ordinary endotoxin absorbtion."

3. Kenneth Taylor advances a mechanical theory. According to him the Bacillus welchii acts upon the carbohydrates of the muscles and forms gas. The latter, being entrapped in the fascial sheaths, causes an increase in pressure (at times as high as 23 pounds or 1.5 atmospheres). The bloodvessels are thus compressed, producing a local ischemia with consequent necrosis. Putrefactive organisms now invade the tissues and digest them.

4. Conradi and Bealing divide the process into two stages, namely: (*a*) The formation of lactic, butyric, propionic and succinic acids from the muscle carbohydrate causes the edema and necrosis; (*b*) the saprophytic stage follows in which the spore bearing organisms bring about putrefaction.

5. Sir Almroth Wright believed that the essential factor is an acidosis, both local and general, the former being more pronounced. Bacillus welchii, furthermore, is able to reduce the antitryptic power of the blood and tissues and also to produce acids. Thus, since this organism grows best in acid media, a vicious circle is established. An acid imbalance was actually found by Wright in the blood of 24 cases of gas gangrene.

6. Bull advanced the theory that the "Bacillus welchii infection is not a blood invasion of the microörganism and not an acid intoxication, but an intoxication with definite and very potent poisons pro-



duced by the growth of the bacilli in the tissues of the body . . . the poison (an exotoxin) is a complex of a hemolysin and another poisonous body." The latter acts locally upon the tissues and blood-vessels bringing about edema, necrosis and probably a general intoxication.

Pathology. Gas gangrene is essentially a disease of devitalized tissue, the favorite location being damaged muscle. Other structures such as bloodclot, blood serum, lung, liver, and spleen may be involved. The spread of infection is along the longitudinal

axis and runs up and down the wounded muscles from the seat of the lesion. According to the French, it spreads along the vessel sheaths as well. Single muscles are thus affected from end to end; while adjacent muscles may not be involved. When, however, the main blood supply has been cut off, as for instance, when the femoral artery has been blocked in the thigh, the whole limb dies and undergoes gas gangrene. Especially prone to involvement are injured muscles contained in inelastic compartments as exemplified by the anterior tibial group. This is quite apparent in the Bellevue series where 58 per cent of the cases of gas gangrene following compound fractures occurred in those of the tibia.

The muscle is usually markedly swollen and changed in color. As a rule, the first color change[18] resembles brick-red. Later, it becomes a yellowish-green. The end stage is a greenish-black with a glistening surface. Frequently, as described by Kenneth Taylor.[19] air spaces separate distinct groups of fibers. On section, the sensation is that of cutting through well-aërated lung. Fat-free tissue thus infected usually floats in water. Along the muscle sheaths, one may observe a small amount of thin sero-pus. The escaping gas gives off a heavily sweetish odor and is inflammable. Microscopically, one finds early vacuolization of the nuclei and swelling of the individual fibers which stain irregularly. In the more advanced stage, the fibers are widely separated. Eosinophils and occasionally polymorphonuclear leukocytes may be found between the widely separated fibers. The last stage shows "complete dissolution of muscle fibers . . . merged into a more or less homogeneous mass of eosinophilic débris showing numerous air spaces and diffusely infiltrated with bacilli."

Cardiovascular System. Taylor[19] observed at autopsy that the larger veins and the heart frequently contained considerable gas. The vascular intima is stained a deep red. In one of the five Bellevue autopsies of gas gangrene the endocardium, valves, and aorta showed marked hemolysis; the entire aorta being uniformly stained a dark red. Occasionally, the larger bloodvessels are thrombosed. Histologically, the intima is often eroded and sometimes shows sloughing. The connective tissue may be undermined and an escape of blood into the perivascular tissues take place causing a discoloration of the skin.[19]

Liver. Three cases at autopsy showed the liver enlarged, light red in color, soft and fragile in consistency. On section, the surface gave the impression of having been subjected to cooking. The normal lobular markings were absent. In portions the liver was honeycombed with bubbles of air.

Adrenals. Van Gehuchten,[20] experimentally inducing gas gangrene in guinea pigs, demonstrated marked hemorrhagic lesions in the suprarenal glands. Taylor[19] reports the presence in human adrenals of marked medullary congestion with occasional hemorrhage. The adrenals were negative in the Bellevue autopsies.

Symptomatology. The usual type of injury in civil practice is either a lacerated wound contaminated by street dirt or an apparently clean gunshot wound. Subjectively, there may be no complaint, although in most of this series pain was the most prominent symptom (due, no doubt, to the nature of the injury *per se*). According to Taylor,[21] pain of short duration followed by numbness of the part involved is very suggestive of gas bacillus infection. This was most strikingly demonstrated in the first of the 2 cases that follow.

Usually, the mental condition of the patient, despite the pain, remains unaffected. There is a definite sense of well-being. At times the infection may be far advanced and yet the patient may fail to display any apprehension. Sir Almroth Wright[22] has stated that even in fatal cases of gas gangrene the patient remains with clear intellect and without suffering to the end.

A careful inspection of the injured part is important. Wounds into which foreign bodies have been introduced must be carefully watched for the earliest signs of gas gangrene. This is especially imperative in compound fractures. Unexplainable swelling of the affected area should give rise to suspicion. The swelling is tense and distinctive, differing from the fluctuation of an abscess and the pitting of edema.

The color changes, as described by Wallace,[18] are of aid in the diagnosis. Very early, the skin is normal in color. Later, it appears tense and is unusually pale, these changes being the result of edema. A dirty cream-colored hue supervenes and is followed by the appearance of purple-stained areas. The latter enlarge, swell, then in turn collapse. The margins of these stained areas are quite distinct, though irregular, the unstained intervening skin being colored a grayish-white. Serosanguinous blebs now put in their appearance to be followed shortly by the dark greenish-yellow tint of the final stage. Occasionally, one may find bronzing of the skin, though Tenopyr[23] believes that slight bronzing of the skin will be seen frequently if the affected area is viewed in good light (provided the wound has been sewed tightly). The latter was observed in 1 of our patients (Case I) on the day of admission.

The discharge is distinctive. It is serohemorrhagic, thin, and there is very little pus formation. The odor, too, is quite characteristic. It is peculiar, putrefactive, disgusting and indescribable. Once having smelled a case of gas gangrene, one can never forget it. During the war it was referred to as the "death smell."

The crackling sensation imparted to the fingers is one of the cardinal signs. Yet, not only may it be absent in the more virulent infections but also it is a comparatively late sign. Nor is it infallible! Gas bubbles may be seen to escape when pressure is made with the flat of the hand in the direction of the wound. Before ascribing crepitus to the presence of gas bacillus infection, traumatic (that is, surgical) emphysema must first be ruled out. This should not be

difficult in civil practice, since cases are seen within an exceedingly short time after the injury, usually in less time than the shortest period of incubation. Hence, if crepitus be present on admission and the other signs of gas bacillus infection be absent, the condition may be considered that of traumatic (surgical) emphysema.

As pointed out by the French, tenderness along the course of the main bloodvessel supplying the affected area is of value.[24]

The Roentgen ray has been mentioned as an aid to early diagnosis. Gas in the soft tissues gives a characteristic picture, appearing as sharply defined bright areas on the positive and dark on the negative. In doubtful or suspicious cases early and repeated Roentgen rays may be of value. Here, too, one must be careful to rule out surgical emphysema as well as normal shadows, as for instance, those of bursæ or of the popliteal space.[25]

Clinical Data. The temperature is usually low at first while the pulse is rapid, the increase of the latter being proportionately greater than the rise of the temperature. A sudden rise in temperature shortly after the reduction of a compound fracture should give rise to a suspicion of gas gangrene. In this series, the average temperature on admission was 100.6° F. with an average pulse of 111. The respirations were correspondingly quickened though, according to Challiers,[26] "dyspnea has a greater prognostic significance than a diagnostic value."

Cornell,[27] experimentally inducing gas bacillus infection in rabbits, found a gradual rise of the leukocyte count, associated with a lowering of the red blood cell count and a characteristic and almost constant anisocytosis. A definite leukocytosis was present in most of our cases, the average count being 17,360. The lowest was 9280 and the highest 27,400. The polymorphonuclear leukocytes were proportionately increased, the average being 83 per cent. The lowest was 60 and the highest 91 per cent. A moderate anemia was also present. The urine was in most instances normal, though occasionally glycosuria was present as noted in the first of the case histories that follow.

Smears should be taken in all suspicious cases. Cultures, however, are of doubtful value. The interval required for a report is valuable time lost. Furthermore, a negative result may mean nothing, whereas a positive finding does not necessarily mean gas bacillus infection, as was demonstrated by Taylor.[19] Of 216 war wounds that he studied, 61 per cent were positive for Bacillus welchii by culture but only 35 per cent of the positive developed gas bacillus infection. Nevertheless, when associated with symptoms of gas gangrene, a positive anaërobic culture makes the diagnosis conclusive.

In a comprehensive survey of the literature, we found only 12 cases of positive blood culture reported. The rarity of the latter may possibly be due to the oxygen in the circulating blood. As a

rule, if invasion take place, it occurs at or just prior to death at which time a condition of diminished oxygen content exists, a result of the failing circulation. Baugher,[28] in 1914, reported 4 cases with positive blood cultures, 3 of whom recovered. Taylor[19] quotes an instance of a positive blood culture present shortly after operation for gas gangrene of the thigh that became negative forty-eight hours later. His explanation was that the invasion was temporary and resulted from the incision of bloodvessels of the thigh. Possibly, this may account for the presence of a positive blood culture in Baugher's nonfatal cases. In the few instances where blood cultures were taken in the Bellevue series, the results were negative.

Treatment. The outstanding contributions of the World War toward the treatment of gas-bacillus infection were first, débridement and second, serotherapy. Tenopyr,[23] however, maintains that Martin Tinker of Ithaca described débridement as early as 1909 and that "this form of treatment was used in the Kings County Hospital from that time on." Perhaps no better outline of treatment could be evolved than the instructions issued to the United States medical corps prior to the battle of Chateau Thierry in 1918.[29] In substance they are:

1. Operate as early as possible.
2. Use nitrous oxid-oxygen anesthesia if possible.
3. Prepare the part with a minimum amount of delay and trauma.
4. Avoid tourniquets.
5. Make incisions longitudinally and half again as long as that thought necessary both in skin and fascia.
6. Go between (rather than through) normal muscle and do not cut across them unless it be unavoidable. Better a long separation between two than a short cut across one.
7. Leave as much skin as possible.
8. But open the wound thoroughly and freely.
9. Excise all torn, crushed, discolored, noncontractile muscle until there is left only that which is firm, of normal color, actually contractile, and which bleeds readily.
10. Make a careful and conscientious search for and remove all loose bone and foreign bodies, especially clothing and bloodclots.
11. Stop the bleeding, leave the wound wide open, and separate its walls with wet gauze *laid* in, not packed in.
12. Use Carrel tubes if it be certain that they will be properly cared for. Otherwise, omit them.
13. Use plenty of dressings and make careful splint fixation of the part.
14. Do it all as rapidly as is consistent with good technique.

Nitrous oxid-oxygen anesthesia is to be recommended instead of ether because it is less likely to produce a further fall in the blood pressure. Cannon,[30] experimenting on animals, found that

etherization until the wink reflex disappears usually causes a fall of 30 to 40 mm. of mercury. Nitrous oxid-oxygen in a ratio not exceeding 3 to 1, when pushed to the same degree of anesthesia, may be without any fall in the blood pressure. A previous dose of morphin, furthermore, is of value in producing a satisfactory anesthesia.

Of late, the introduction of spinal anesthesia bids fair to replace nitrous oxid-oxygen in selected cases. In this connection, Cabot's experience[31] is instructive. With ether anesthesia, his mortality rate in 90 carefully controlled cases of amputation of the thigh was 66 per cent, whereas with low spinal anesthesia it was reduced to

TABLE III.—RESULTS OF TREATMENT—40 EXTREMITY CASES—CURES: 50 PER CENT.

Treatment.	No.	Cures.	Per cent.
Nonintervention	6	1	17
Débridement only	11	4	36
Amputation only	17	10	60
Débridement followed by amputation	6	5	83

33 per cent. According to Labat[32] "the chief contraindication to intraspinal block is a very low blood pressure, that is, below 100. Even then, if it is expected that the condition of the patient will not be benefited by the administration of any other form of anesthesia, spinal anesthesia can be induced, provided a subcutaneous injection of the caffein compound stimulant is made at the same time, repeating the dose if necessary. Patients in a state of shock or toxemia need only local infiltration with or without the association of a first-stage narcosis."

It is the consensus of opinion that the Carrel-Dakin treatment or its modification is, if properly carried out, the method of choice for wounds infected by the gas bacillus. Indeed, any oxidizing agent is of value. Some prefer Wright's hypertonic salt solution or hydrogen peroxid or a solution of quino-formol as suggested by Pilcher.[2] It is best to reduce the dressings to a minimum or, if possible, to expose the wounded area to direct sunlight, that is, to afford the wound free access to the oxygen of the air. Should it be impractical to secure the latter, light and heat may be provided by means of a cradle as ordinarily employed in the treatment of burns. Thus, a condition of continuous hyperemia is induced, increasing thereby the oxygen supply to the affected area.

Table III shows graphically the results of various methods of treatment in the Bellevue extremity cases. Nonintervention gave the highest mortality rate (83 per cent). It must be noted, however, that most of these cases were severely injured and that they might have died from the injuries alone. With débridement alone, 64 per cent of deaths occurred and with amputation alone, the mortality was 40 per cent. Débridement followed by amputation showed the happiest results, but 17 per cent dying.

Serotherapy. Specific antisera in the treatment of gas gangrene were first used during the World War. Several varieties were employed as, for example, those of Weinberg, Vincent, Leclainche and Vallee, and Bull and Pritchett. All were given an extensive trial and according to Major John Everidge[33] "personal experience leads to the belief that in many cases it appears to attenuate the virulence of the infection and to render certain cases more amenable to surgical procedures than would otherwise have been the case."

Sacquepee[34] treated 191 cases of proven gas bacillus infection with Leclainche and Valle's polyvalent serum. He reported a mortality of 13 per cent contrasting with a death rate of 75 per cent in a controlled series of nontreated cases. Duval and Vaucher[35] were able by employing Weinberg's mixed serum to reduce the mortality from 16 to 3.15 per cent. Vincent,[10] too, reports excellent results from the use of his own mixed sera. It is of interest to note that most of this work was done by Europeans.

As a prophylactic agent, serum gives even more encouraging results. Sacquepee[34] administered prophylactic injections to 319 severely wounded. Only 4 cases (1 per cent) developed gas gangrene; whereas in a controlled series of nontreated cases the morbidity rate was 7.2 per cent. According to Vincent[10] not a single case of gas gangrene came to his notice among the severely wounded who had received the serum in preventative titer. Van Beuren,[29] quoting Elser, states, "on the whole, the results (of prophylactic injections) were encouraging, and it is believed that if the armistice had not interrupted the progress of the tests, a very favorable report might finally have been rendered which would have dictated the employment, as a routine measure, of the antigas serum in our (U. S. A.) armies." Bull[36] on the other hand, found that the active treatment of gas gangrene by antitoxin was disappointing. In a letter to G. E. W. Hardy he stated, "The practical side of gas gangrene antitoxin was disappointing. It would probably do some good as a preventive if given when injury occurs."

It must be emphasized that, to date, serum treatment of gas gangrene has in no way replaced surgery. The principles of treatment as enumerated above must be adhered to whether serum be or be not injected. In 1918, the Fifth Interallied Surgical Conference for the Study of War Wounds[29] concluded that, though preventive and curative serotherapy have both given encouraging results, surgical treatment "is still indicated and in no way modified."

The first requisite in successful serotherapy is the use of a mixed or polyvalent serum. A monovalent serum is in most instances of little value in view of the fact that the organisms causing gas gangrene are rarely found in pure culture, there being a definite tendency to symbiosis. Furthermore, it is not sufficient to pool two or more specific sera obtained from animals separately immunized against the various gas-producing organisms. To secure the

best effect one must employ a polyvalent serum obtained by injecting into the same animal a mixture of the various pathogens. This, possibly, may account for Bull and Pritchett's unfavorable results since they administered a monovalent serum.

Method of Administration. Intravenous injection in combination with intramuscular injections proximal to, but in the neighborhood of, the wound is the method of choice. Ivens[37] advocated the dilution of the serum with normal saline solution and its administration subcutaneously to prevent anaphylactic shock. Relatively few cases of anaphylaxis, however, have been observed. In the third and most successful of his series Ivens used an initial preventive dose of 10 cc. of Leclainche and Vallee polyvalent serum with 30 cc. of Weinberg and Seguin's triple mixed sera. If symptoms of gas gangrene developed, he gave repeated doses. Ivens advocated as a further precaution the administration of additional sera, given in fractional doses, as a preliminary to secondary operations in all infected cases.

For prophylaxis, Sacquepee[38] injected from 40 to 80 cc. of antivibrion septique and antibellonensis sera, half intramuscularly in the vicinity of the wound and half subcutaneously at some distance from it, repeating the procedure in twelve hours. As a curative measure he used (in the edematous form) 80 cc. of antibellonensis, half subcutaneously and half intravenously; and 20 cc. of antivibrion septique serum subcutaneously, repeating the injection in from four to six hours, and again in from sixteen to twenty hours. In the gaseous form, he administered from 30 to 50 cc. of each serum, again half intravenously and half subcutaneously.

In civil practice, serum has been used but little. In all the literature but few cases have been reported wherein surgical treatment was supplemented by serotherapy.[23, 39, 40] The question may be raised whether in these or in other cases cures would not have been obtained without the use of serum. Judging from the results during the war, it seems likely that the use of a serum (preferably polyvalent) in civil practice would materially reduce the mortality from gas gangrene. Tenopyr[23] treated 24 cases with tetanus perfringens antitoxin serum. He reports a mortality of 7 cases (29 per cent). This may be compared with a mortality rate of 46.5 per cent in our series of 85 cases not treated with serum.

Case Reports.—CASE I.—Male, aged twenty years, admitted August 8th and discharged September 24, 1926. Chief complaints were swelling, numbness, pain and loss of function of left forearm. On the night of August 8th after drinking one pint of whisky, he went to bed apparently normal. Upon awakening the next morning, his left forearm and hand were swollen, numb, slightly painful and paralyzed. Several hours later, blisters appeared on the arm and hand. His condition becoming rapidly worse, he entered the hospital.

NOTE.—According to patient's mother the condition of the arm on arrival home, the night previous to admission, was about that seen in the ward.

Admission note: Swelling, cyanosis, and coldness of left forearm from elbow to fingers; tense and indurated swelling; fingers blackened few blebs present; burned odor of skin and hands; radial pulse present; no evidence of dislocation or fracture; blood pressure in left arm, 158 systolic and 90 diastolic, and right arm 132 systolic, 100 diastolic mm. of Hg. Ward Roentgen ray was negative for fracture or dislocation.

FIG. 1.—Case I. Gas gangrene of left upper extremity. Before débridement. Note the dusky hue, edema and bleb formation. (No. 1.)

FIG. 2.—Case I. After débridement. Note the extensive destruction and free exposure of soft parts. (No. 2.)

The next day, the paralysis of the left extremity was definite. Loss of sensation was absolute. The edema had spread to the middle of the arm. Only the thumb and index fingers could be moved. The extremity was warm and the radial pulse still present and of good quality. By evening the swelling had extended to the left shoulder. Wet dressings of magnesium sulphate were applied. The edema became less marked but gangrene was increasing and the odor became disagreeably foul. On the fifteenth, definite air crepitus was obtained just below the elbow, localized to a small area, and a culture from one of the blebs was positive for Bacillus welchii. The next day, at operation, the radius and ulna were found to be entirely denuded of periosteum. There was a partial avulsion of

skin which was gangrenous. Considerable pus and gas were present in the tissues. The muscles were necrotic and gangrenous.

Technique. Necrotic skin was entirely removed. Muscles were widely separated and pus pockets opened. Twelve Dakin tubes were inserted throughout the musculofascial planes. Irrigations were instituted with hydrogen peroxid and Dakin's solution. Following operation, the arm was soaked twice a day in a weak solution of potassium permanganate. Within eight days considerable sloughing had taken place about the elbow. In the meantime daily cultures were reported positive. In spite of this treatment,

FIG. 3.—Case I. Well-healed stump following amputation. Radical operation done fifteen days after débridement because of spread of gas bacillus infection. (No. 3.)

the condition became markedly worse, so that on the thirty-first, fifteen days following the first operation, his arm was amputated at the middle of the humerus. A culture from the stump seven days later was negative. Recovery was uneventful.

Clinical Data. The temperature was septic. Roentgen ray findings were negative. The urine was positive for sugar on one occasion. On admission, the leukocytes numbered 13,200 with 88 per cent polymorphonuclears. A similar count was obtained on two successive occasions. The blood chemistry was normal. The blood Wassermann and the blood culture were negative.

CASE II.—Male, aged thirty-nine years, in moderate shock, admitted August 20, 1926. Chief complaint was pain in both legs

due to injury, the pain being worse in the left. The injury was sustained when a truck struck him and ran over both his legs. Physical examination was negative except for local condition. Two large lacerations were present over the middle of the left tibia through which muscle protruded. Bleeding was profuse. There was no evidence of fracture of bone. A provisional diagnosis of laceration of leg with rupture of muscle was made. One Dakin tube was inserted and the wound Dakinized every six hours.

Three days later, the blood showed a moderate anemia and 500 cc. of blood were transfused. The wound was examined daily for crepitus and five days following the injury definite air crepitus was

FIG. 4.—Case II. Note the healing granulation tissue about the site of the gangrenous muscle. (No. 1.)

felt. At this time, the muscle and skin were gangrenous and necrotic and a thin pus could be expressed from under the skin. The odor of gas bacillus infection was present. Amputation was advised but refused. Débridement was therefore done on the same day.

Findings. Gangrenous skin, gas and fluid pus in the tissues; blackening and necrosis of the gastrocnemius and other flexor muscles; sloughing of the subcutaneous tissue. The periosteum was denuded from the anterior surface of the tibia.

Technique. The gangrenous skin was removed. The affected muscles were widely opened and the sloughs separated. Deep incisions were made through the subcutaneous tissue. Ten Dakin tubes were inserted and Dakinization was performed every three hours.

The day following, an anaërobic culture was reported positive for Bacillus aërogenes capsulatus. Daily, every nook and crevice of the wound was flushed with boric acid, followed by hydrogen peroxid

and then thoroughly Dakinized through the tubes. The leg was dressed with paraffin gauze and with a light wet bandage. Several days later a footlight was added to the treatment. Excessive granulations at the margins of the wound were kept down by topical applications of 20 per cent silver nitrate. About two months after injury, the tibia was thoroughly covered with healthy granulation tissue and sloughing had ceased in great measure. The area was now skin grafted (the opposite thigh being utilized for the longitudinal grafting). An excellent result was obtained. With the aid of a plaster cast full extension returned.

Previous to skin grafting an attempt was made to secure full extension of the leg under gas-oxygen anesthesia. This proved unsuccessful, flexion recurring within a day.

FIG. 5.—Case II. Excessive granulation tissue controlled by application of 20 per cent silver nitrate. (No. 2.)

Clinical Data. The temperature was septic until the twenty-fifth day after admission. The urine and blood Wassermann were negative. Roentgen ray findings revealed evidence of an osteoperiostitis of the shaft of the tibia. On admission, there were 9200 white blood cells with 86 per cent polymorphonuclear leukocytes. Four days later, the count was only 7400 with 60 per cent polymorphonuclears. Two weeks later, the count was 10,200 and 89 per cent polymorphonuclears. The red blood cells numbered 3,670,000 with a hemoglobin of 80 per cent.

CASE III.—Female, aged forty-six years, admitted May 4th and on ward at time of preparation of paper. Brought to hospital immediately after falling five stories. On admission, patient was in shock. Physical and Roentgen ray examinations disclosed (1) laceration of neck, (2) fracture of third lumbar vertebra, and (3) compound fracture of right tibia and fibula several inches above the

ankle. About the latter area crepitation was felt. This was believed to be surgical emphysema. Neurologic examination revealed evidence of a transverse block at about the third lumbar segmental level.

Soon after admission, the wound of the compound fracture was débrided and cleansed with green soap, peroxid and ether, and finally Dakinized. A temporary splint was applied to the extremity. Progress for the next four days was satisfactory. On May 8th four days after injury, it was noticed that the area about the compound fracture was swollen, that the ecchymosis had spread from the toes to the knee, and that a foul odor emanated from the wound. The next day she was taken to the operating room and a laminectomy performed, as well as débridement of the affected leg.

Findings and Technique of Débridement. Dead, necrotic tissue with a characteristic odor of gas gangrene. There was no crepitation. The muscles were necrotic for a distance of 3 to 4 inches, this necrosis extending upward above the posterior tibial vessels and nerves. Excision of dead tissue was attempted and the wound was left open with a long posterior incision. Loose pieces of bone were removed and the wound Dakinized. Cultures from the depth of the wound were reported positive the next day (May 10th). On the latter day, crepitation was present above the area previously incised and a disarticulation at the knee joint was therefore done. The patient reacted badly to the anesthesia; but the postoperative recovery was good. At present (June 10th) the patient is doing nicely and the stump has healed.

Clinical Data. The temperature was low (100° to 101° F.) except for a rise to 102° F. following the first operation, dropping to 99° F. in two days. The pulse ranged from 100 to 130; respirations were twenty-two to twenty-four per minute. Urine was negative. On admission there were 10,500 white blood cells with 76 per cent polymorphonuclears. Six days later, the white count rose to 16,000 with 83 per cent polymorphonuclears. On that day the red blood cells numbered 1,970,000 with a hemoblobin of 50 per cent. Several days later the red blood count was 2,580,000 and the hemoglobin, 60 per cent.

Summary. 1. Eighty-five cases of gas gangrene in civil practice are herein reported.

2. Bacillus welchii is the predominating organism.

3. The incidence in the Bellevue Hospital series in a period of fifteen years was one in 7310 cases (0.0001 per cent).

4. Mortality in the total series was 45.9 per cent. In 40 extremity cases the mortality was 50 per cent.

5. The average incubation period was three days.

6. Gas gangrene is essentially a disease of devitalized tissue the favorite site being damaged muscle.

7. The anterior tibial group of muscles is especially prone to involvement due to their tense fascial sheaths.

8. Gas crepitation must not be mistaken for traumatic (surgical) emphysema.

9. The color changes, the thin serohemorrhagic discharge and the peculiar odor are characteristic.

10. Tenderness along the course of the main bloodvessel of the affected area may be of value in the diagnosis.

11. As a rule the pulse-temperature ratio is disturbed, the pulse being relatively increased. A definite leukocytosis and moderate anemia exist.

12. Only 12 cases of positive blood culture are reported in the literature. There were none in the Bellevue series.

13. Briefly, treatment is as follows: Operate early; use gas-oxygen anesthesia or, if possible, spinal anesthesia; make long longitudinal incisions between and not through normal muscles; excise damaged tissue until muscle that is firm, contractile, of normal color, and that bleeds easily is encountered; leave wounds wide open and Dakinize.

14. In the Bellevue series best results were obtained with early débridement followed by amputation.

15. War results speak for serotherapy, though at present the latter cannot supplant surgery. In civil practice, serum has been but little employed. The use of a polyvalent serum as an integral part of the treatment of gas gangrene is advocated.

NOTE.—We wish to thank Dr. George D. Stewart, Director of the Third Surgical Division of Bellevue Hospital, for permission to quote the above data and Dr. Arthur M. Wright for his kind advice and helpful criticism.

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STOVARSOL (SPIROCID) POISONING.

Report of Six Cases.

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The increasing use of stovarsol in a number of infections and its tendency to produce untoward reactions mark it as a drug which should be well known generally.

Since its introduction in 1922 for the treatment of syphilis, it has been administered also in amebiasis, lambliasis, malaria and yaws, as well as in chronic malnutrition for its general tonic effect. The most extensive application has been in the treatment of syphilis, especially in France and Germany, where much difference of opinion exists on its value in comparison with the other arsenicals. Judging from the few reports of the treatment of malaria with stovarsol, it adds very little to the control of this disease. On the other hand, the intestinal parasitoses seem to be definitely influenced and the effect on yaws dramatic.

This paper, however, is concerned chiefly with toxic reactions following the administration of stovarsol. I have found only five reports calling attention particularly to this phase of the subject, though reactions have been noted by many of those reporting experience with the drug.

The Drug. Stovarsol was first synthesized by Ehrlich in 1909 in the course of his work on the arsenicals. Preparation 594, as it was designated, was obtained in crystalline form and tested therapeutically in the series of experiments which finally produced arsphenamin, but was discarded on account of its toxic properties and weak effect in syphilis. Apparently casting about for an arsenical which could be given orally in the treatment of syphilis, Treufouel in the laboratory of Fourneau of the Pasteur Institute reëxamined this preparation in 1921, feeling that its former failure was due to impurities. The following year Levaditi[1] and his coworkers introduced the presumably improved drug as stovarsol for the treatment of syphilis. In this country, it was admitted to New and Nonofficial Remedies[2] in 1926, as a remedy against amebiasis, but specifically not recommended in the treatment of syphilis; chemically it is an organic arsenic preparation, acetyloxyaminophenylarsenic acid, containing 27 per cent arsenic.

According to German authors, it is identical with spirocid manufactured there by Höchster Farbwerke. It is made in this country by Powers, Weightman, Rosengarten Company, under license of Les Etablissements Poulenc Freres, Paris. Apparently all three firms market the 0.25 gm. (4 gr.) tablets for oral use.

Reports of Reactions. Mention of undesirable effects is present in nearly every report of its use in a series of 10 or more cases, including one or several of the following manifestations: Coryza, bronchitis, sore throat, malaise, aching, chill, fever, skin eruption, jaundice, adenitis, diarrhea, abdominal pain, eosinophilia and albuminuria.

In the original paper of Levaditi[1] and his collaborators, 3 of 16 cases presented toxic symptoms; the first, transient fever which did not interfere with continued treatment, the second, mild skin erythema, and the third, after 16 gm. (256 gr.) of the drug in twenty-five days, an intense exanthem lasting a month and considered analogous to arsphenamin dermatitis. In the following two years,

1923 and 1924, others, especially in Germany, began to use the drug. Hoffmann[3] saw a rash "similar to a salvarsan eruption" which cleared up quickly after the use of sodium thiosulphate. Krösl,[4] using stovarsol in one group of syphilitics in primary and secondary stages and spirocid in another, 1 gm. (16 gr.) per day on alternate days, encountered reactions in 2 of the stovarsol-treated cases (total number not given) and in 2 of 73 patients receiving spirocid. One stovarsol reaction came after 7 gm. (112 gr.) had been administered, the other after 12 gm. (192 gr.). Both spirocid reactions appeared after 7 gm. The manifestations were on the whole similar, with fever from 38.3° C. (100.9° F.) to 39.9° C. (103.8° F.) and erythematous generalized rash varying from scarlatiniform to maculopapular. He also observed a rise in temperature after the first gram given to primary syphilitics, which, subsiding under continued treatment, was considered a Herxheimer phenomenon. This initial febrile reaction has been commented on by Lehner and Radnai[5] and by Luerssen,[6] who also has observed transient accentuation of the luetic rash.

Early in 1925 Kromayer[7] laid emphasis on 2 reactions in 8 luetics treated by him with spirocid, 1 gm. (16 gr.) on alternate days. While the secondary syphiloderm disappeared in three or four days as a rule, the drug reaction appeared on the ninth day of treatment after 4.25 gm. (68 gr.) in 1 case and on the eleventh day after 5.5 gm. (88 gr.) in the other; both had fever to 40° C. (104° F.) and painful swollen lymph glands, followed by a generalized intense erythema which was purpuric in places, all subsiding within a few days after discontinuing the drug. He also mentions Bory's patient who, after 16.75 gm. (268 gr.) of spirocid, developed a rash of a month's duration, resembling an arsphenamin reaction. A little later Bruhns and Picard[8] reported the use of spirocid in 48 cases and stovarsol in 5; 6 of the former group and 1 of the latter developed a mild rash, either macular, papular or urticarial, without fever or subjective symptoms and clearing up promptly when the drug was stopped. The stovarsol reaction appeared after 7.25 gm. (116 gr.) were taken. Altmann and Eliassow[9] administered either drug carefully to 15 luetics in doses of 1 to 3 tablets of 0.25 gm. (4 gr.) daily for three to six days in a course, repeated after equal rest periods, in no case allowing a total of more than 16 gm. (256 gr.). They observed 4 instances of albuminuria, several of mild skin erythema and 1 of jaundice which, however, may have been of syphilitic origin. One patient who had had a persistent skin reaction after arsphenamin and a recrudescence after an injection of novasurol, developed, after one tablet of stovarsol, severe persistent exfoliative dermatitis. Heymann,[10] comparing stovarsol and arsphenamin, considered the latter much more toxic; in the case of the former, however, he mentions the production of fever, abdominal pain with or without diarrhea, erythematous skin reactions and once

dermatitis resembling that of arsphenamin, lymphatic enlargement and rarely jaundice. Izar[11] likewise called attention to the hypersensitiveness of some individuals to the preparation. More recently Sézary and Barbé,[12] in treating paretics with stovarsol, observed a skin eruption in one patient and fever in another, attributed to the medicine.

The case of Schwarz[13] warrants emphasis on account of marked susceptibility to the drug. His patient, having accidentally received syphilitic blood in the eye, was given stovarsol prophylactically and the initial dose of one tablet of 0.25 gm. (4 gr.) was given at 8 P.M. He was awakened at 11 P.M. by intense itching and found a skin rash. On the second day, 3 tablets were taken, increasing the itching and rash, which was papular, in places urticarial, and generalized except for the face and neck. On the third day, no stovarsol was taken, there was edema of the hands, headache, fever to 39° C. (102.2° F.) and the rash persisted. The reaction was gradually subsiding by the eighth day when 2 more tablets were taken, the temperature rising again to 39° C. that night. On the ninth day, headache and fever recurred and he had diarrhea with green stools; on the tenth and eleventh days, the lymph nodes, especially inguinal, were painful and swollen in addition to the other symptoms. The reaction was again subsiding on the twelfth day, the skin being nearly clear except for petechiæ, possibly from scratching. When a blood count was done on the sixteenth day, hemoglobin and red cells were normal, white cells 6500 with a differential count of 52 per cent polymorphonuclears and 17.5 per cent eosinophils; twenty-one days after onset, the eosinophilia was 10 per cent and on the twenty-seventh day, 3 per cent.

The treatment of amebiasis with stovarsol was started by Marchoux,[14] when, in 1924, he reported a series of 59 cases with success in all but 2 and apparently without untoward reactions, though in some instances 2 tablets were administered daily for several weeks following the initial course. Johns and Jamison,[15] among 27 cases of amebiasis given 0.75 gm. (12 gr.) daily for seven days, saw 3 reactions; 1 patient complained of dull headache, another developed a mild rash and the third slight fever and rash. These authors[16] later reported experience with a total of 46 cases without mentioning unfavorable effects, though as many as 8 such courses were administered to one individual. Silverman,[17] giving a dose of 3 tablets daily for ten days to 6 patients, observed no reactions, but among 10 cases receiving 50 tablets each in the same manner he noted "definite arsenical poisoning" in 2. Sixty-four cases of chronic amebiasis were treated with stovarsol by Brown,[18] giving 3 tablets daily for six days and repeating the course with slight modification after about two weeks; 4 of them developed mild skin erythema. The rash reappeared on one of the patients when the drug was

administered again after the interruption. He noted that symptoms of an upper respiratory infection preceded the appearance of the rash by two days, considered it incidental, and advised against the use of stovarsol during a "cold." One individual took from 4 to 6 tablets daily up to a total of 70 (17.5 gm. or 280 gr.), without trouble. Harrison[19] reported more in detail the only reaction he saw among 40 cases of chronic amebiasis treated with stovarsol. After receiving 3 tablets daily for ten days, his patient exhibited coryza, lacrimation and malaise; the following day a morbilliform eruption and typical Koplik spots appeared; all symptoms disappeared in four days following discontinuation of the drug and injection of sodium thiosulphate intravenously. The dose was decreased and no ill effects were encountered in subsequent cases.

The most striking report of the toxic effects of stovarsol is that of Morgan,[20] who observed three reactions, one of them severe, in giving the drug to 8 cases of amebiasis. The first, after having received emetin injections, was given 3 stovarsol tablets daily for seven days, a total of 5 gm. (80 gr.). On the seventh day, the temperature rose to 39.8° C. (103.6° F.), the following day cough and coryza appeared and on the ninth day a generalized macular roseola appeared. Thiosulphate was given on the two following days and symptoms subsided in a week. The leukocyte count on the fifth day of the reaction was 5400. The second was not given emetin but received a similar course of stovarsol and on the sixth day had a fever of 37.4° C. (99.2° F.), on the seventh 37.7° C. (99.8° F.) with malaise and anorexia, on the eighth 38° C. (100.4° F.) with headache, a morbilliform rash and mild itching; the course was similar to the first on withdrawal of the drug. At the height of the reaction the leukocyte count was 6400. The third patient had acute amebiasis and after 3 emetin injections received 2 gm. (32 gr.) of stovarsol in the course of five days, at the rate of 1 or 2 tablets daily. On the fourth afternoon, she had generalized aching but took the tablets that evening and the following morning, when she had a chill, fever to 38.3° C. (101° F.), backache and sweating. On the sixth day, though the drug had been withdrawn, all symptoms were worse and she was seriously sick with fever to 40° C. (104° F.). Though the temperature decreased next day after the use of thiosulphate, the rash became petechial and did not recede until the ninth day, following which recovery was uneventful. Leukocyte counts were 9000 and 14,500; unfortunately differential counts were not reported and the probable eosinophilia not determined. In discussing Morgan's paper, Meleney mentions three toxic reactions; one of these patients, given stovarsol on account of arthritis and the presence of Endameba dysenteriæ cysts in the stools, died of arsenic poisoning after taking 0.5 gm. (8 gr.) daily for nine days. This is the only reported fatality from the administration of stovarsol; unfortunately more details are not given.

In the use of the drug as a general tonic in the treatment of non-syphilitic nurslings, Oppenheim[21] encountered 4 instances of scarlatiniform erythema and fever and several more without rash but with green diarrhea among 250 cases treated. Selwyn-Clark[22] observed rapid striking improvement of yaws in 21 African natives and encountered no other toxic symptoms but rather frequently occurring diarrhea; he administered from 2 to 4 stovarsol tablets daily, reaching a total of 4 gm. (64 gr.) in a week and repeating the course after a rest period. Stovarsol was found of distinct value in a selected group of syphilitics by Cregor and Gastineau,[23] who observed only occasionally headache and slight fever as toxic phenomena. This incidentally is the first report in this country of its use as an antisyphilitic remedy; as in the case of bismuth, its application may be expected to increase.

Report of Cases. Unlike the toxic manifestations cited above, which though falling into one group apparently have varied greatly, the 6 instances of stovarsol poisoning that I have had experience with have followed a rather constant course. The reaction is often ushered in by a day or two of coryza or sore throat with "grippy" feeling of malaise and muscular aching. During this period, fever usually appears, rises with the appearance of the rash and falls as it fades. Enlargement and tenderness of the lymph glands, especially in the neck, and the eruption are sometimes the first symptoms noted by the patient, at other times come on after a day or two of the premonitory respiratory symptoms. The rash tends to be generalized with no constant site of predilection; it is erythematous with at times purpuric areas; it may be macular or papular, fine or coarse, and resembling either scarlet fever or measles respectively; there may be urticarial characteristics and a good deal of itching. No definite desquamation was noted and gastrointestinal symptoms have been of little prominence in this series. In the 4 cases in which blood counts were done, there was a leukopenia of from 3250 to 5200; in 3 of these the eosinophil count, previously within normal limits, rose to 6 or 7 per cent, but in the fourth case went no higher than the 3 per cent eosinophilia which was present before treatment. No serious cases were encountered; withdrawal of the drug and symptomatic measures were the only remedies necessary and recovery was usually complete in from one to two weeks; in 1 case recurrence of symptoms appeared.

Case Reports. CASE I.—Mrs. T. W., aged thirty-six years, lived in the Philippines and China between the ages of twenty-five and thirty-one years. In that period, she had two attacks called amebiasis in which there were malaise, anorexia, loss of weight and afternoon fever but no gastrointestinal symptoms. Amebæ were found in the stools both times and she underwent strenuous courses of emetin hypodermically and ipecac orally. Symptoms were

improved and stools negative after each course. While in the Orient and for the five years following, exhaustion and easy fatigue had been persistent and brought her for examination April 30, 1924. Family and past medical histories were irrelevant.

Examination was normal except for signs of mild hypothyroidism and moderately infected tonsils without enlargement of cervical glands.

Laboratory findings included: Blood count, April 30, 1924; hemoglobin, 70 per cent; erythrocytes, 4,700,000; leukocytes, 6400. Differential count: Polymorphonuclears, 66 per cent; lymphocytes, 28 per cent; endothelials, 5 per cent; eosinophils, 1 per cent. The urine was normal chemically and microscopically. Basal metabolism rate 13 per cent below theoretical normal. The blood Wassermann was negative. The stools showed no amebæ or other parasites in 6 specimens between May 1, 1924 and August 6, 1925.

Treatment and Reaction. No satisfactory improvement followed a thorough trial of thyroid gland administration and antiamebic treatment was considered justifiable on the history. Since it was impossible for her to give up for emetin treatment, stovarsol 0.25 gm. (4 gr.) three times daily was started August 6, 1925.

The patient had taken about 21, 0.25 gm. tablets, a total of 5.25 gm. (84 gr.) by August 14, when she noticed soreness in throat and tenderness in sides of neck and felt "grippy." When she reported August 15, temperature was 37.8° C. (100° F.), the cervical glands were moderately enlarged and tender and the throat was uniformly reddened and edematous. The drug was discontinued. The following day she felt better and was not seen. On August 17, she had generalized aching, especially in the back muscles, temperature 38.9° C. (102° F.), and the rash appeared for the first time. At its height, there was a marked blotchy deep erythema involving the whole body except the face and scalp, most marked over back and extremities; as the finger was passed lightly over the skin, slight unevenness was apparent; itching was intense, dermatographia marked, and lesions in some areas mildly urticarial in appearance. The superficial nodes were all moderately enlarged and tender. Blood count on August 17 was: Leukocytes, 3950; differential: polymorphonuclears, 51 per cent; lymphocytes, 31 per cent; endothelials, 9 per cent; eosinophils, 6 per cent; basophils, 3 per cent. The urine was normal except for a faint trace of albumin. The reaction had gradually subsided by September 3; afebrile, throat normal, no adenitis, skin normal except for excoriations on thighs from scratching. Toward the end of the reaction, small amounts of bloody mucus were discharged from the nose. There were no digestive symptoms attributable to stovarsol.

CASE II.—Mrs. E. N., aged twenty-five years, came for examination July 16, 1925, complaining of indigestion of five years' duration;

this consisted chiefly of lower abdominal distention and rumbling with a good deal of belching and flatus, mild constipation of six months' duration, no diarrhea. She had become nervous and easily fatigued and had lost 12 pounds (5.4 kg.) weight, though taking extra food. Family and past medical histories were irrelevant except for a short stay in Mexico two months before and while there had a ten-day attack of fever, the nature of which was undetermined.

Examination was negative except for moderate undernutrition and faulty posture.

Laboratory findings included a blood count, July 16, 1925: Hemoglobin, 76 per cent; erythrocytes, 4,875,000; leukocytes, 8850. Differential count: Polymorphonuclears, 63 per cent; lymphocytes, 33 per cent; endothelials, 4 per cent; eosinophils, 0. The urine contained a faint tract of albumin; normal otherwise, microscopically and chemically. The blood Wassermann was negative. The stool in two specimens contained active flagellates identified as giardia.

Treatment and Reaction. In addition to measures to correct posture, stovarsol 0.25 gm. (4 gr.) three times daily was started July 18, 1925. She had taken nearly 25 tablets, 625 gm. (100 gr.), when on July 25, she noticed soreness of the cervical glands and had fever of 37.8° C. (100° F.); a throat specialist said she had glandular fever. Stovarsol was discontinued. On July 26, she stayed in bed and felt better but was more active next day, felt sick, and temperature rose to 38.9° C. (102° F.). Dr. Ralph Rabinowitz, who took care of her during the reaction, was called in on July 28. He found the posterior cervical nodes mildly enlarged and tender, throat diffusely reddened and causing a good deal of discomfort, a scarlatiniform rash most marked over the neck and upper chest, petechial spots on the soft palate, and temperature of 37.8° C. (100° F.). The urine was normal. The rash had subsided by July 31, and the temperature gradually returned to normal by August 2. On August 3, rash and fever recurred for four days, but were less marked. August 4: Leukocyte count, 5200. Differential count: Polymorphonuclears, 42 per cent; lymphocytes, 48 per cent; transitionals, 2 per cent; eosinophils, 7 per cent. There were several mild recurrent febrile periods with skin eruption; the adenitis gradually subsided. A subsequent stool examination disclosed no parasites.

Case III.—Mr. C. R., aged fifty-one years, was examined April 26, 1926, on account of indigestion of three years' duration. Onset was gradual and distress chiefly gaseous distention of upper abdomen after meals and during the night, causing palpitation. A year before he was first seen, he had an attack of painless diarrhea lasting two weeks. Subsequently he had very little indigestion until five months before he was examined when his symptoms recurred, asso-

ciated with mild constipation, easy fatigue and loss of 17 pounds (7.6 kg.) in weight. Family and past medical histories were irrelevant; he had never been out of this country.

Examination revealed moderate malnutrition, pyorrhea, a systolic murmur over the mitral area but no other evidence of circulatory disease, visceroptosis and moderate distention of the colon.

Laboratory findings included a blood count, April 26, 1926, normal except for an eosinophilia of 3 per cent. The urine was normal. The blood Wassermann was negative. Gastrointestinal Roentgen ray examination showed a low atonic stomach, no evidence of ulcer or gall-bladder disease; barium enema revealed colon gas-distended and atonic but no organic defect. The stool contained Endameba councilmania and chilomastix (State Hygienic Laboratory).

Treatment and Reaction. Stovarsol therapy was started May 10, 1926. He had taken 3, 0.25 gm. (4 gr.) tablets daily, a total of 6.25 gm. (100 gr.), when on May 19, he had headache, felt "grippy," and found his temperature to be 38.9° C. (102° F.). He stopped the drug but was in bed four days, during which a skin eruption developed, and he had mild sore throat and diarrhea. This patient was out of town and was not seen but described the rash as generalized, "bright red, like measles," most marked on trunk and legs. In addition, he reported soreness and enlargement of cervical glands. Blood count was not made. In a stool of October 20, 1926, Endemœba dysenteria and Endemœba councilmania were reported. According to a letter, February 13, 1927, he was considerably improved, until recently there has been recurrence of flatulence.

CASE IV.—Mr. G. K., aged twenty-two years, came for examination April 21, 1926, on account of crampy pains about the umbilicus of three weeks' duration, worse at night but never severe, not associated with vomiting, diarrhea or other digestive symptoms. During this period he lacked his usual energy, had frontal headache and dizziness and had lost 7 pounds (3.2 kg.) in weight. Family and past medical histories were negative; he had never been out of California.

Examination showed moderate undernutrition, mild superficial lymphadenopathy, hypotension with blood pressure systolic 94, diastolic 70, but no other evidence of circulatory disease; in the abdomen a moderately gas-distended cecum but no tenderness or spasm, low right kidney; general examination otherwise normal.

Laboratory examinations, April 22 to 24, 1926 showed: Blood count: Hemoglobin, 87 per cent; erythrocytes, 4,700,000; leukocytes, 5500. Differential count: Polymorphonuclears, 60 per cent; lymphocytes, 32 per cent; transitionals, 4 per cent; eosinophils, 4 per cent. The urine was normal. The blood Wassermann was

negative. The stools contained Endameba councilmania (State Hygienic Laboratory).

Treatment and Reaction. After improvement on regulation of his habits of eating and living, on May 7, 1926, stovarsol was prescribed, 0.12 gm. (2 gr.) three times daily for three days, then the full 0.25 gm. tablet three times daily; he took about 20 tablets and reported on June 14, 1926, that he felt much better and had had no untoward effect from the drug. One stool specimen was negative.

He next reported on February 16, 1927, that he had continued in good health until three weeks before, when the abdominal symptoms reappeared. He had a few tablets remaining from the previous course and on February 12 took 0.12 gm., on February 13 and 14 took three 0.12-gm. doses daily and on February 15 two doses, a total of 1.12 gm. (18 gr.). On arising on February 16 he felt "grippy" and noticed an eruption on the face and chest; the throat and cervical glands felt sore. When seen at 5 P.M. the same day there was a generalized, irregular, mottled, erythematous eruption, most marked over back, least prominent on the legs; in some areas it was slightly papular and urticarial and there was moderate dermographia. During the examination, he fainted and the rash almost completely disappeared, reappearing as his circulatory tone improved. There was general glandular enlargement, most marked in the neck, involving both anterior and posterior chains, some of which reached the size of an almond; the adenopathy involved also the axillary, inguinal, suboccipital and epitrochlear nodes. The throat was diffusely reddened. Temperature was 37.3° C. (99° F.). Examination was otherwise unchanged. A blood count on February 16 was: Leukocytes, 5200; polymorphonuclears, 67 per cent; lymphocytes, 28 per cent; transitionals, 5 per cent; eosinophils, 0. The following day, February 17, he felt better, the rash was fading, but there was slight itching for the first time; the glands were smaller and less tender; throat less inflamed; temperature normal; leukocyte count, 4650, with a similar differential count excepting for 3 per cent eosinophils. The urine was normal. Rash and pharyngitis had completely cleared up by February 25, but the adenopathy not completely cleared by March 3. The abdominal symptoms cleared up during the reaction, probably chiefly with control of diet and activity; there was no diarrhea or other symptom of gastrointestinal irritation by the drug. No parasites were found in the stools.

CASE V.—Miss L. D., aged twenty-seven years, reported November 29, 1926, on account of nervousness, lack of energy, migraine and recurring anemia since childhood. There were no digestive symptoms; appendectomy had been done in 1915. Family and past medical histories were negative; she had lived in various parts of the United States but had not been out of the country.

The examination was essentially negative.

Laboratory findings were: Blood count: Hemoglobin, 70 per cent; erythrocytes 4,290,000; leukocyte and differential counts normal. The urine, basal metabolism, gastric analysis were normal. The blood Wassermann was negative. The stool contained many amebic cysts identified as Endameba histolytica.

Treatment and Reaction. In addition to general treatment, it was considered advisable to eradicate the amebic infection. Stovarsol was started December 5, 1926. She took 0.12 gm. (2 gr.) doses three times daily for the first three days, then the full 0.25 gm. dose without untoward results until she had taken about 20 tablets, 5 gm. (80 gr.), over a period of eight days. At this time, there appeared generalized aching, feeling of fever and a slight sore throat for a day. She continued to take the tablets and the following day a generalized rash appeared, which she considered similar to measles, associated with a good deal of itching; at this time the glands on the sides of the neck were enlarged and tender. There was nausea but no vomiting or diarrhea. She discontinued the tablets; in the next two days the temperature reached 37.8° C. (100° F.), the rash faded but continued to itch, and the glands decreased in size and tenderness. The reaction had completely subsided in a week and no residua were found when she was next seen on December 31, 1926. Since she had notified no one during the attack, a blood count was not made. No parasites were found in one stool obtained since stovarsol administration; the patient's symptoms continue to vary a good deal under treatment, as they have for years.

CASE VI.—Miss G. F., aged thirty-four years, became a patient February 14, 1927, on account of intestinal flatulence with sense of pressure and distress in the left hypochondrium, nervousness and insomnia of ten years' duration. There had always been moderate dysmenorrhea. Family and past medical histories were irrelevant; she had spent most of her life in San Francisco and had never been out of this country.

On examination the patient was found to be a dark-complexioned, emotionally unstable Jewess, with a good deal of vasomotor instability in the skin, and moderate acne; atonic abdominal walls, visceroptosis and borborygmi and splashing with pressure over the colon. Proctoscopic and general examination were essentially negative otherwise.

Laboratory findings included a blood count: Hemoglobin, 70 per cent; erythrocytes, 4,600,000; leukocytes, 6300. Differential count: Polymorphonuclears, 67 per cent; lymphocytes, 27 per cent; transitionals, 4 per cent; eosinophils, 2 per cent. Urine, gastric analysis and basal metabolism, normal. The blood Wassermann was negative. A barium enema revealed a movable colon

which dropped below the iliac crests in the upright position, but no other abnormalities. Stools contained the cysts of Endameba councilmania (State Hygienic Laboratory).

Treatment and Reaction. Stovarsol was started February 24 when she took two doses of 0.12 gm. (2 gr.) each; the following three days she took three such doses daily; from February 28 to March 3, when the drug was stopped, full doses of 0.25 gm. (4 gr.) three times daily were taken. A total of 17½ tablets were used, 4.3 gm. (70 gr.). On March 2 and 3 she ached and thought she had grippe; on March 4 there was tenderness over the cervical and axillary glands and very little sore throat. On the morning of March 5 she noticed a rash and when seen later in the day this was a dark, blotchy, slightly raised erythematous eruption confined to the back, upper chest and forearms. It was most marked on the back while on the forearms it consisted of fine papules. The superficial glands were all moderately enlarged, especially the upper anterior cervical nodes which reached the size of a hazelnut, tender, soft and discrete. The throat was diffusely reddened; no Koplik's spots were seen. The temperature was normal and the leukocyte count 4350 with polymorphonuclears, 74 per cent; lymphocytes, 16 per cent; transitionals, 4 per cent; eosinophils, 6 per cent. The following day, March 6, the rash was generalized, excepting on face and neck; the hands and feet were moderately swollen and cyanotic; she complained of intense burning and itching, especially in the extremities; glands and throat were unchanged and the temperature was normal. A leukocyte count was 3250, with polymorphonuclears, 60 per cent; lymphocytes, 25 per cent; transitionals, 9 per cent; eosinophils, 6 per cent. Though she continued afebrile and the pharyngitis and adenitis cleared up, the rash and discomfort associated with it varied from time to time, probably largely influenced by her nervous and vasomotor instability, and did not leave for about ten days. At one time a slightly enlarged spleen was felt; there were no other changes in the general examination. Former digestive symptoms continued unchanged during the reaction. This patient received sodium thiosulphate orally and intravenously without apparent effect on the reaction.

Summary. Reactions of a toxic nature during the administration of stovarsol are of sufficient frequency and severity to be borne in mind when it is prescribed. The skin eruption probably is the manifestation most often encountered; at any rate it is the one which attracts notice. As nearly as can be judged from the reports of those observing the rash, it occurs in about 7 per cent of patients receiving the drug, with or without other symptoms. At present it is impossible to estimate the incidence of the less striking symptoms. Unfortunately, the source of my material is such that I cannot state the frequency of reactions among cases treated. Comparable to the experience of others, I observed lesser symptoms such as

headache, malaise, sore throat, coryza and slight fever which promptly disappeared when the drug was withdrawn. The leukopenia and eosinophilia are noteworthy and probably depend largely on skin involvement.

The symptoms of stovarsol poisoning, as I encountered them, appear as a rather constant picture. In my experience, this syndrome differs materially from the untoward effects of the arsphenamins as well as those of inorganic arsenic preparations and is characteristic of stovarsol. Though in this series there has been no tendency of the skin reaction to progress to the severity of exfoliative dermatitis, several instances have been reported and I have heard of a patient left with this distressing condition for many months.

The question of cause and prevention of toxic manifestations during the administration of stovarsol is an important one. Undoubtedly, individual susceptibility to the drug is a factor, probably the most constant and unfortunately the least controllable. The case of Schwarz,[13] in which the reaction started within three hours after one tablet was taken, is the most striking; the patient of Altmann and Eliassow,[9] who developed dermatitis after arsphenamin and novasurol as well as stovarsol, undoubtedly was hypersensitive to arsenic compounds. Morgan's[20] third case had a severe reaction starting even before 2 gm. (32 gr.) of the drug had been taken.

The manner of administration of the drug apparently has very little to do with the frequency of untoward symptoms, though in general it can be said that the smaller the dose, the fewer the reactions. Different authors have given stovarsol in doses of from 1 to 6 tablets a day, either daily or on alternate days, up to a total dose of from 6 to 16 gm. (96 to 256 gr.) in from three to thirty days; some advise its use in courses of three to seven days with similar rest periods intervening. Unusual tolerance was demonstrated by the patient of Brown[18] who took from 4 to 6 tablets daily for a total of 70 without trouble; Marchoux,[14] who was not bothered by intolerance of the drug, gave 2 tablets daily for several weeks after a more intensive program at the start. Excluding the cases such as those cited above showing unusual idiosyncrasy, symptoms of poisoning have been noted most frequently after stovarsol had been taken for several days, usually from six to fourteen, and after an average total of 6 gm. (96 gr.). In this series the average total dose was 4.6 gm. (73 gr.) and the onset of symptoms in seven days. The first 3 cases received three whole tablets daily from the start and the last 3 only after two or three preliminary days of half-tablet doses; the latter group came down with their symptoms as quickly as the former.

This brings us to practical points which should be borne in mind when treatment is instituted. Of foremost importance is the

recognition of early toxic symptoms and either the daily observation of the patient or his careful acquaintance with them. With the onset of prodromal signs the drug should be promptly withdrawn. In my own experience and in that of other authors, this is all that is necessary, though sodium thiosulphate has at times been administered. Referring again to the serious poisoning seen by Morgan and by Schwarz, and to some of those cases going on to exfoliative dermatitis, continuation of the medicine after the appearance of untoward symptoms undoubtedly was a factor. Stovarsol should not be used on patients who have previously shown an idiosyncrasy to other arsenicals; accordingly, it cannot be considered a safe remedy in syphilitics for whom arsphenamin has proven toxic. There is little to be added to the matter of dosage; probably the first few days of treatment on half doses is a safer way to recognize those unusually sensitive so that treatment can be stopped after the smallest possible amount of the drug. Patients, such as Case VI of this series, whose skin vasomotor mechanism was unusually labile and who had had eruptions from small amounts of sodium bromid, should be given stovarsol with great caution. Apparently the nature of the condition for which it is given has no bearing on the reaction. Finally all three preparations, the French, German, and the American, are probably equally culpable.

Conclusions. Stovarsol (spirocid) is a useful remedy in a number of infections and its use may be expected to become more general.

It produces undesirable symptoms with considerable frequency; although a variety of manifestations have been reported, there are certain outstanding signs such as fever, skin eruption and adenitis which appear quite constantly as a syndrome characteristic of stovarsol poisoning. Though reactions are usually mild, some exceptionally severe ones have been reported, including exfoliative dermatitis and one fatality.

While individual idiosyncrasy is the most important cause of ill effects from the drug, the consideration of lesser factors such as selection of cases for its use and the dosage is important. The acquaintance with and recognition of the early toxic symptoms is essential in prescribing stovarsol since in most instances prompt discontinuation is all that is necessary to avoid serious poisoning.

I am indebted to Dr. Herbert C. Moffitt for the opportunity to report these cases and to Dr. Ralph Rabinowitz for his notes on one of them.

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ACUTE AND RECURRENT PSEUDOAPPENDICITIS DUE TO INTERCOSTAL NEURALGIA.*†

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Many clinicians who are wide awake to avoid appendectomy for pain and tenderness of long standing in the right lower abdominal quadrant are caught napping by the same pain and tenderness when these are remittent, intermittent or recent in development, and urge immediate appendectomy. They do not seem to realize that chronic pseudoappendicitis in its incipiency simulates recent acute or subacute appendicitis and that operation is just as strongly

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† This paper is supplementary to my paper, "Chronic Pseudoappendicitis," published in last month's issue of this Journal and to which the reader is referred for information that is vital for a proper understanding of the present paper.

contraindicated in the earlier acute stages as in the later chronic stage. Acute, subacute, recurrent and relapsing pseudoappendicitis are common affections and, as a rule, are due to intercostal neuralgia usually of toxic origin. The parietal location, the extent and the areas of the tenderness in the more acute forms of pseudoappendicitis are determined by the same tests as in the chronic form. Many clinicians who are unaware that the tenderness is parietal in chronic pseudoappendicitis recognize the parietal location of the tenderness in acute pseudoappendicitis, but they ascribe its presence to a visceroparietal sensory reflex due to a true appendicitis.

Papers appear from time to time in which writers describe the skin hyperesthesia symptom of acute appendicitis. They are describing a limited phase of the more extensive picture which I claim is due to parietal neuralgia.

Sherren[1] wrote one of the earliest papers on cutaneous hyperesthesia in appendicitis. He ascribes the visceroparietal sensory reflex to nerve irritation caused by tension and not by inflammation within the appendix as indicated by 8 cases in which the superficial tenderness disappeared with the occurrence of perforation or gangrene. In over 20 cases of early appendicitis without skin tenderness on which he operated he found perforation or gangrene in the appendix without exception. Out of 51 cases of localized appendiceal abscess only 5 exhibited superficial tenderness. In 3 of the 5 the skin tenderness persisted for several days after the operation. He found skin hyperesthesia present in 40 of the total of 125 cases of acute appendicitis that he examined.

Robinson[2] found hyperalgesia in only 26 of the 123 cases of acute appendicitis that he examined. He found that tension within the appendix was not the cause of the superficial pain in some cases. He also found cutaneous hyperesthesia almost as frequently with abscess as without abscess.

Ligat[3] is an adherent of the theory of the visceroparietal sensory reflex, and believes it originates in the mucosa.

Cope[4] found hyperesthesia of greater or less extent in 110 out of 185 cases of acute appendicitis. He writes: "Though perhaps more common with an unperforated distended appendix, it was quite frequently found with a gangrenous or ruptured appendix, or an undistended unperforated viscus. Abscesses in the first few days of their formation were also frequently accompanied by hyperesthesia of more limited extent. The position and extent of the hyperesthesia varied greatly. In nearly all the cases it was limited to the right side of the abdomen, but in 8 cases it was bilateral." In 1 of his cases the hypersensibility was present on the left side only.

In a recent very instructive paper on the disturbed reflexes in acute appendicitis, Robertson[5] gives an excellent description of the ways in which rigidity occurs and remarks that he has failed more

often than he has succeeded in demonstrating cutaneous hyperesthesia in acute appendicitis, but he finds it more commonly in chronic catarrhal appendicitis.

The antagonistic views of the various writers on skin hyperesthesia are further emphasized by a comparison of the divergent diagrams of skin hyperesthesia illustrating their papers.

Livingston[6] has written one of the most recent and most enthusiastic papers on the value of skin tenderness, as shown by a twisting pinch test in the diagnosis of acute appendicitis. He based his studies on the "appendix triangle" bounded by three lines connecting the umbilicus, the right pubic spine and the highest point of the right iliac crest. Tenderness mainly outside the above area, he states, indicates lesions of other viscera. The appendix triangle does not signify either the complete or the sole skin area ever involved in cases with appendicitis; it does signify an area of clinical limits, and hyperesthesia confined to these borders is caused, in his experience, by no other intraäbdominal condition than primary or secondary involvement of the appendix. By "positive skin signs for appendicitis," he means hyperesthesia present on the anterior abdominal wall, confined to the appendix triangle and maximal at its center. Positive cutaneous hyperesthesia limited to the appendix triangle was present in 317 instances (86 per cent) out of 367 cases in which the diagnosis of acute appendicitis was confirmed. In all instances in which the skin signs were negative a perforative or gangrenous appendicitis was found, but he does not specify the number of these cases. He emphasizes, as I do, that strong grades of stimuli are necessary in eliciting skin signs. He states that the sign of positive cutaneous hyperesthesia, limited to the appendix skin triangle, was found to be of more value than any other sign or symptom in the diagnosis of acute appendicitis.

My experience with skin tenderness leads to conclusions different from those expressed by Livingston. For instance, I have found his "positive skin signs for appendicitis" in dozens of patients from whom the appendix had been removed, hence I cannot concede that they are caused solely by a primary or secondary involvement of the appendix. The fact that Livingston and some other writers do not find skin tenderness in perforative and gangrenous appendicitis seems to me to be a fact of great significance. They state, or assume without giving much detailed authority therefore, that tenderness is present early in every case, but that it disappears when actual necrosis or abscess formation occurs. The commonly expressed theory is that with actual death of the appendix the dead nerves contained in it are no longer able to transmit the impulses which gave rise to the visceroparietal reflex. This theory sounds plausible, but I think it is fallacious in assuming that skin tenderness was present in the early stage. If it be conceded that the appendix or its nerves can give rise to a visceroparietal sensory

reflex, then it must be granted that other viscera or their nerves can do the same. It would, therefore, seem reasonable that in cases of gangrenous appendicitis the visceroparietal reflex would be continued by the nerves: (1) In the stump of the appendix, if only part of its length be destroyed; (2) in the cecum, if the appendix die *in toto*. Livingston makes no mention of having tested for cutaneous hyperesthesia after operation, but Sherren, Cope and others have observed, and I have frequently noted, that it persists for a few days after appendectomy. It seems most inconsistent to claim that death of the nerves in gangrenous appendicitis will immediately abolish cutaneous hyperesthesia when operative removal of the same nerves by appendectomy requires the lapse of several days to effect the same results. The theory of "dead nerves" seems at fault also in the cases of perforation and abscess formation, because neither of these processes commonly causes a complete destruction of the nerve supply to the appendix. My own findings as to skin tenderness being almost invariably absent in these very frank and unquestionable types of acute appendicitis have helped in my arriving at the conclusion that the viscero-parietal sensory reflex is a myth, not only as regards the appendix but other viscera as well. Furthermore, the absence of skin tenderness in these undoubted cases of acute appendicitis adds conviction to my belief that skin tenderness is a symptom of pseudoappendicitis, and that its occasional association with true appendicitis is nearly always accidental rather than resultant. The skin tenderness of intercostal neuralgia is a very common symptom, and the elements of chance inevitably lead to its occurrence with a fair degree of frequency in conjunction with any other common disease, such as appendicitis, warts or ingrown toenails.

In view of the various writers not giving more details as to their findings in the major group of their cases, which they simply designate as "acute appendicitis" and from which they have excluded their cases of perforation, gangrene and abscess, I cannot but suspect that in a very considerable percentage of their cases they have gotten the cart before the horse, and that their diagnoses of acute appendicitis have been greatly influenced by their findings of skin tenderness. Having made their clinical diagnosis of acute appendicitis in so many of these cases of parietal tenderness, it seems improbable that they have taken the precaution to check up their findings by microscopic confirmation.

There is a certain fallacy about "acute appendicitis" which I think is fairly prevalent. The surgeon makes a clinical diagnosis of acute appendicitis; he is disappointed at operation in not finding gross evidence of acute inflammation; he theorizes that the condition is one of "colic" or that his manipulation has relieved a "kink" before the appendix was brought into view or that some other amelioration has recently occurred; the excised appendix is sent to

the pathologic laboratory; the patient leaves the hospital "cured" within a week or ten days; the pathologist reports that he finds such and such evidence which he regards as indicative of "chronic appendicitis;" and the incident is then apt to be closed by the busy surgeon thoughtlessly commenting on the clinical diagnosis of "acute appendicitis" having been confirmed by the microscope. A tremendous flood of light would be thrown on the subject of acute appendicitis if all clinicians would adopt the policy I have put into effect, of asking the pathologist to make a specific report on the presence or absence of microscopic evidence of acute inflammatory changes in each and every appendix that is sent to him from the operating room. The pathologist's preliminary sentence very commonly reading to the effect, "I am unable to find any evidence of 'acute' inflammatory changes in this appendix" would cause the clinician to "stop, look and listen," and make him realize that the pathologist's further report detailing changes of "chronic" appendicitis does not confirm the clinician's preoperative diagnosis of "acute" appendicitis. It is obvious that the two diagnoses are farther apart than if one had been carcinoma and the other sarcoma. The cases in which the clinician says "acute" and the pathologist says "chronic" constitute a very large group which I regard as acute pseudoappendicitis.

The most common underlying cause of acute pseudoappendicitis is an infection of the upper respiratory tract giving rise to a toxic intercostal neuralgia. Various writers, including Hood,[7] Marvel,[8] Behrend[9] and Martin, mention "epidemic" acute appendicitis with onset during or immediately following an attack of influenza or other upper respiratory-tract infection, and some of them state that the abdominal symptoms in these cases are not typical of ordinary acute appendicitis. They believe pyogenic organisms originating at the site of primary infection are conveyed by the blood stream to the appendix, which exhibits "a special tissue susceptibility." Evans[10] is an exponent of this theory, and presents some interesting statistics in support of his views. He found that in a series of 214 cases of acute appendicitis observed during the primary attack that 183 (86 per cent) had shown evidences of acute nasal and throat infections on an average of sixteen days prior to the appendiceal attack. He does not give any details as to operations or pathologic findings in any of his cases.

Warfield[11] reports on "a syndrome in epidemic influenza which simulates very closely acute appendicitis," which he observed during the influenza epidemic at the Jefferson Barracks, Mo., in October and November, 1918. He gives details on 19 cases, in all of which the clinical diagnosis was acute appendicitis, but in several of which operation disclosed only chronic appendicitis. My own observations indicate that the vast majority of the patients who develop abdominal symptoms during either the acute or the termi-

nal stage of infections of the upper respiratory tract have acute pseudoappendicitis and not true acute appendicitis. After antityphoid inoculations in the army camps many soldiers developed symptoms strongly suggesting appendicitis, but Lower and Jones[13] found that a low leukocyte count of 4000 to 5000 established the differential diagnosis.

Acute pseudoappendicitis may occur at any age and in either sex, but is most frequent under thirty years and affects more females than males. The asthenic visceroptotic types are especially susceptible, but the robust are not immune. The abdominal symptoms may arise at any stage of the respiratory infection, but they are commonly delayed until the second or third day after the patient believes that he has fully recovered from one or, more often, two weeks of "sore throat" or "cold" in the head or chest. The history of this infection is usually not volunteered, but is easily obtained by specific inquiry.

By the ordinary tests many of these cases conform to the requirements for true acute or subacute appendicitis. Exceptionally they may have vomiting but nausea is much more frequent; they have pain and tenderness in the right iliac fossa; their pulse is hurried and they have moderate fever and leukocytosis when they first come under my observation which is usually within twenty-four to forty-eight hours after the onset of abdominal symptoms. Nearly all of them have been diagnosed as acute appendicitis by their physicians who refer them for appendectomy. Under the customary examinations for appendicitis there is often a discrepancy in the symptoms or signs indicative of that disease. For instance, the pain and tenderness are often so widespread that they could be accounted for only on the basis of a diffuse complicating peritonitis, and yet true rigidity is absent, and the pulse rate and leukocyte count are not very high. Various other discrepancies may be noted in individual cases.

Patients should be tested for abdominal rigidity before deeper palpation is begun. The presence of true rigidity is almost never encountered in parietal neuralgia, hence its presence very definitely points away from pseudoappendicitis. Absence of rigidity, however, does not contraindicate true appendicitis.

Special tests must be made to separate the false from the true cases of acute appendicitis. The most important is the two-stage test of palpation over the abdominal muscles: (1) While they are relaxed; (2) while they are voluntarily held as tense as possible. Any tenderness elicited over relaxed muscles may be either parietal or intraabdominal in origin. Tenderness which is present, both when the muscles are lax and when they are tense, is parietal in origin, and points to the case being one of pseudoappendicitis. Tenderness which is present with relaxed muscles and absent on vigorous finger-end poking with tense muscles is obviously located

deeper than the anterior abdominal parietes, but its location at or near McBurney's point does not necessarily imply that its source is a tender appendix. In discussing chronic appendicitis, I pointed out that tenderness of lumbar vertebræ and of the right sacroiliac joint are often mistaken for deep appendiceal tenderness. These two sources of possible error can be considered as safely eliminated if the examiner finds exactly the same amount and type of tenderness in applying exactly the same force and form of palpation over the exactly corresponding area of the left iliac fossa. I emphasize the need for exactness in all these points because the average practitioner is prone to be far more diligent in searching the right than the left iliac fossa.

Localized tenderness which is subparietal at or near McBurney's point, and which is not due to tender spine or joint, is most likely due to appendicitis. I do not want to be understood as believing that McBurney's point has any magical association with appendicitis. I believe not only that the major local symptoms of appendicitis are manifested at whatever site the appendix is located, but I go even further in believing that the symptoms are located at the particular site of the particular portion of the appendix that is diseased. By this latter statement, I believe, for instance, that a long appendix, whose healthy base is at McBurney's point and whose diseased tip lies deep in the pelvis, will manifest its symptoms only in the deep pelvis prior to the onset of an extending peritonitis. Surgeons long ago dispelled the myth of the appendix always lying under McBurney's point, and surgeons know that its base is commonly not located at that point, but many physicians do not seem to have grasped this latter fact, which is well illustrated by a series of Roentgen ray films in 56 of their cases of visualized appendix selected at random, which Dr. Henry K. Pancoast and Dr. E. Burvill Holmes placed at my disposal. Those films are so informative that I have had diagrams made to indicate the varying positions of the appendices in relation to the skeleton and to McBurney's and Lanz's points (Figs. 1, 2 and 3).

I believe that the frequently expressed misconception that, irrespective of where the body of the appendix may lie, its tenderness will be manifested at or near McBurney's point, is due to confusion resulting from the tenderness, or more particularly a "tender point," of intercostal neuralgia and the tenderness of lumbar spine and right sacroiliac joint being so commonly encountered at this point.

I concur in the generally accepted belief that in the early stages of acute appendicitis pains are referred first to the epigastrium and then to the umbilical region before they finally localize in the right iliac region. I do not believe, however, that either acute or chronic appendicitis commonly gives rise to symptoms simulating acute or chronic gastric, duodenal or biliary affections. Such supposed simulations are most frequently due to unrecognized intercostal

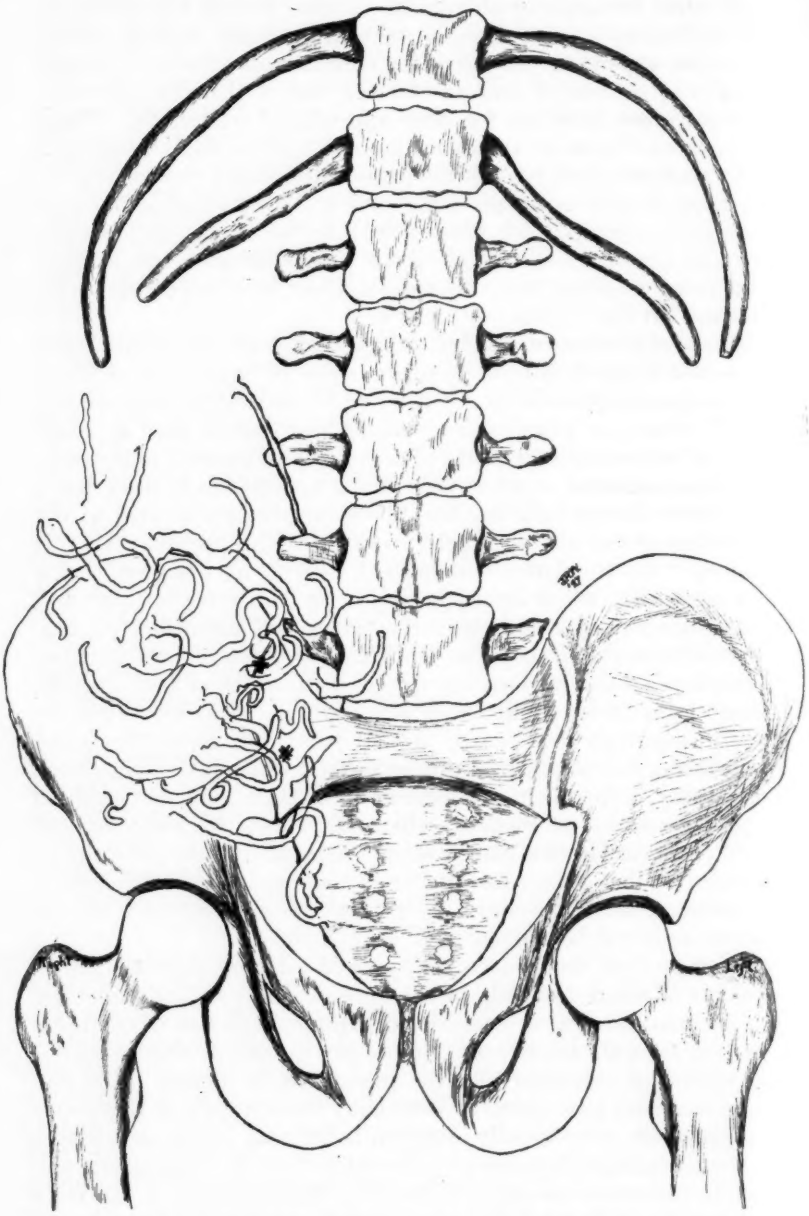

FIG. 1.—Diagram of positions of 24 appendices visualized by barium Roentgen ray examination. Skiagrams taken in the supine posture with Roentgen ray film on the abdomen. Single cross is McBurney's point and double cross is Lanz's point.

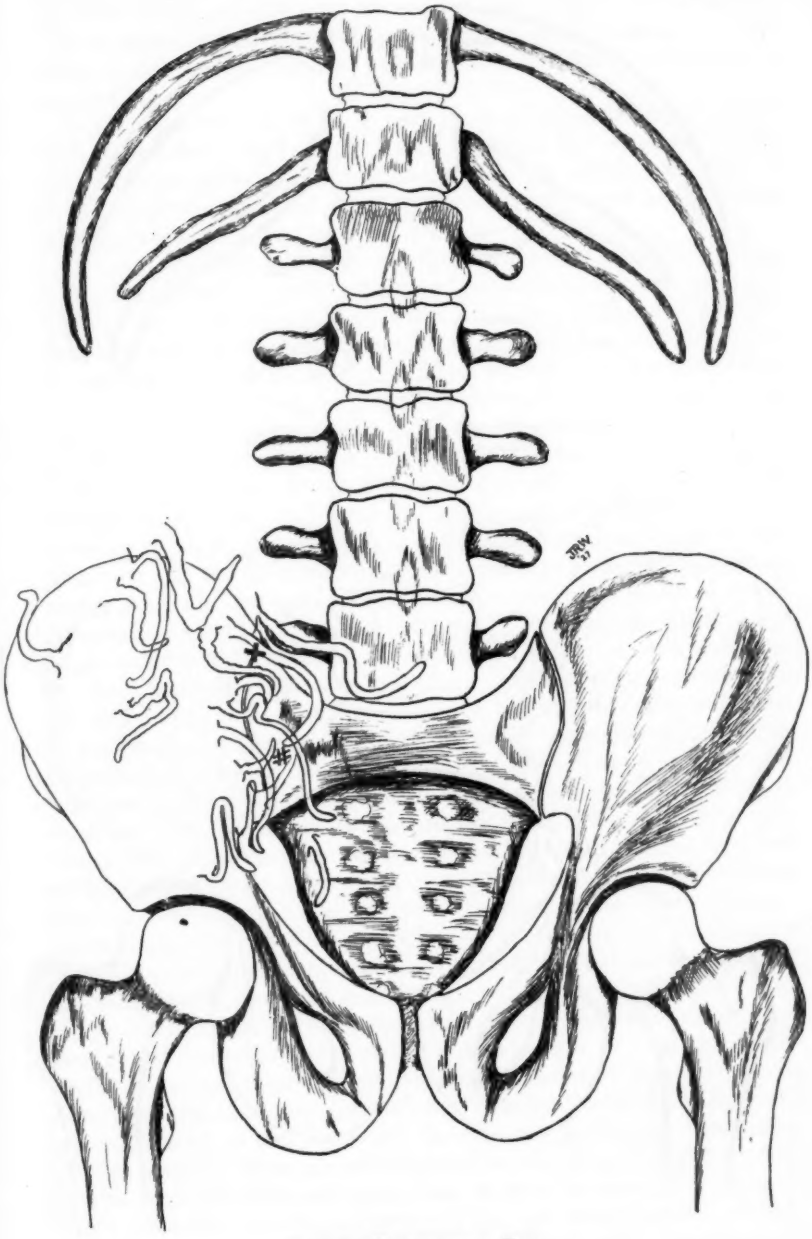

FIG. 2.—Sixteen appendices.

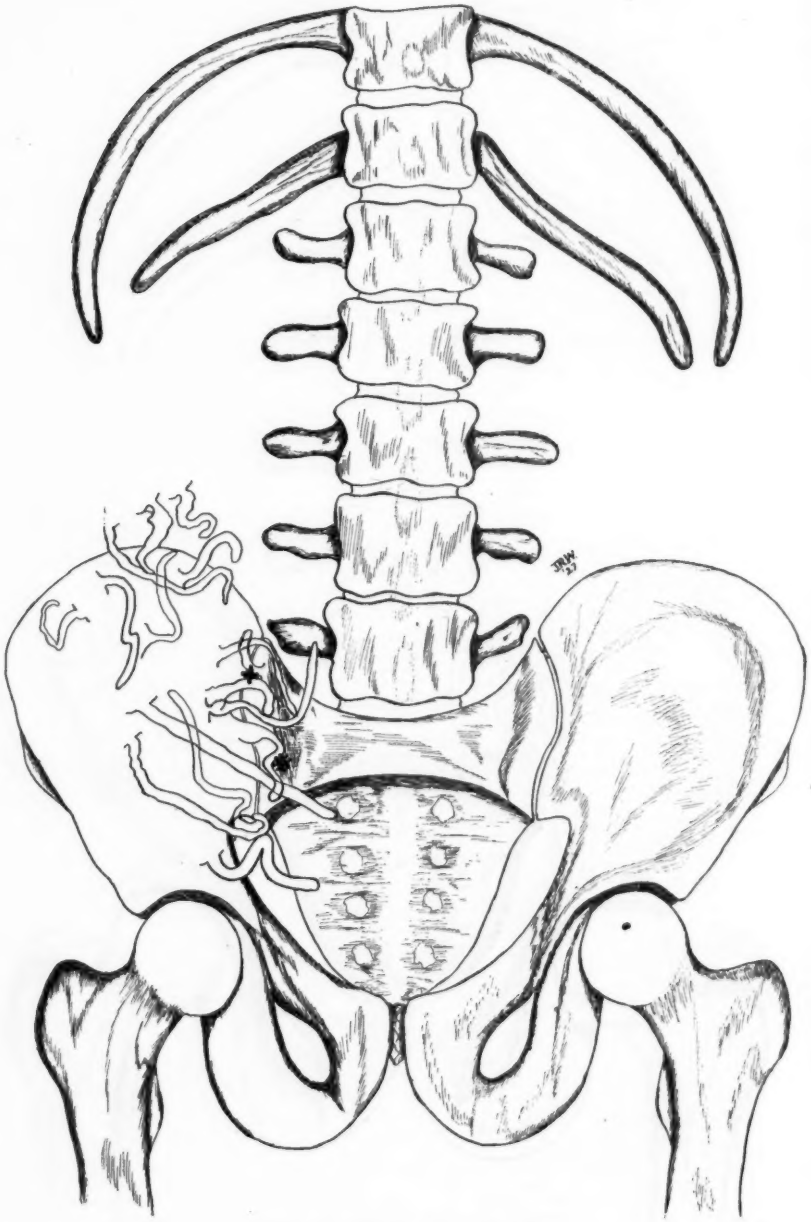

FIG. 3.—Sixteen appendices.

neuralgia of the upper anterior abdominal wall. In commenting on cases of this type, Whiteford[12] makes the cynical statement that "It is usually only after the abdomen has been opened, and the ulcer or gall stones found to be nonexistent, that the appendix is accused."

In the case reports which I have read of left-sided appendicitis with right-sided symptoms, I think it probable the latter symptoms were due to right-sided intercostal neuralgia which was present either in the absence of true appendicitis or as an independent affection coincident with appendicitis.

In the young, true intraperitoneal tenderness at McBurney's point, as a rule, indicates appendicitis, but in patients over fifty years of age the diagnostician had best leave himself a loophole to cover a possible cancer of the large bowel, a low-lying cholecystitis in a very fat patient, or other pathology incident to the later decades of life.

Palpation reveals not only the depth location of the tenderness but also the area of its extent. In cases of intercostal neuralgia it is very often bilateral in the lower abdomen, and is then apt to be mistaken—and even operated upon—for acute bilateral salpingitis. Parietal tenderness may extend over the entire abdomen and the usual method of arriving at an erroneous diagnosis is to fix the blame on the viscus underlying the point of maximum tenderness. Under such circumstances I have seen a diagnosis made of acute pancreatic abscess when the condition was a toxic intercostal neuralgia secondary to pyelitis. Personally, I would as soon endeavor to "read" an individual's mental characteristics from the bumps on his skull, as to make a diagnosis on the basis of the maximal point of parietal tenderness (either directly or as the result of a viscero-parietal reflex) being indicative of a subjacent visceral lesion.

Sensory nerves are distributed to each of the three layers of: (1) Skin and fat; (2) muscles; (3) preperitoneal fat and peritoneum. Flat-finger palpation or finger-end poking over relaxed muscles elicits the combined tenderness of all three layers. Tense muscles prevent demonstration of any tenderness situated in the parietal peritoneum and preperitoneal fat. The amount of tenderness elicited by the same degree of force is therefore habitually less over tense muscles than over relaxed muscles. When tenderness is of equal intensity in each of the three layers the total amount of tenderness demonstrable over tense muscles will be only two-thirds of that obtained over relaxed muscles. Clinical observations indicate that the amount of tenderness located in each of the three parietal layers varies markedly in different patients. Tenderness of the skin-fat layer, as determined by the pinch test, is present in the great majority of cases, but it may be absent in cases in which palpation reveals tenderness of the two deeper layers. These variations are to be expected and have to be carefully considered in arriving at the ultimate decision in certain cases as to whether the

tenderness is located entirely in the parietes or only partly in the parietes and partly within the abdomen.

When parietal palpation tenderness is present in the lower abdomen —as it is in pseudoappendicitis—it will also be found in a bandlike area overlying and paralleling Poupart's ligament and in a V-shaped area in the upper buttock on the same side as I have described under chronic pseudoappendicitis. When the area of palpation tenderness includes the upper abdomen, tenderness will usually be found along the intercostal nerve trunks supplying the area, and it may be either unilateral or bilateral. When nerve-trunk tenderness extends to the upper intercostal spaces there will commonly be found an area of pinch tenderness in skin and fat at the junction of the upper arm with the posterior axillary fold.

Pinching of a liberal fold of abdominal skin and fat between the thumb and two fingers reveals an area of cutaneous tenderness, which varies greatly in size and intensity in different cases and may also vary greatly on succeeding days or in the more acute cases even during the same day. This area of pinch tenderness is commonly larger than the area in which the patient complains of spontaneous pain. Neither the area of spontaneous pain nor the area of pinch tenderness of the abdomen in chronic as well as acute pseudoappendicitis will be found to correspond with the anatomic outlines of any one or more intercostal nerves. My theory for this anatomic discrepancy will be explained in detail in a future paper, but, briefly, it is due to an irritation affecting the terminal branches more than the trunk nerves. The more intense the spontaneous pain the greater, as a rule, is the tenderness found on palpation and pinching. The area of pinch tenderness may involve any one or more of the four quadrants of the abdomen, but is most commonly found on the right side below the level of the umbilicus.

Provided the anterior parietal tenderness is not so great as to prohibit palpation through it of the retroperitoneal structures, there will often be found the two fixed points of tenderness near McBurney's point, due to chronic strain or acute toxic arthritis of the vertebral and right sacroiliac joints. Exactly the same deep tenderness will be found at the two corresponding points on the left side, irrespective of the presence or absence of anterior parietal neuralgia on the left side. Quite often tenderness will be found on making pressure over the transverse processes of vertebræ—especially of the lumbar region—when the spinous processes of the same vertebræ are not tender.

Acute pseudoappendicitis is usually due to an acute toxic intercostal neuralgia. The toxemia—usually from the upper respiratory tract—causing the neuralgia, may, and generally does, give some fever and some leukocytosis.

The similarity of true to false appendicitis is very striking, as determined by the usual long-established methods of examining

for true appendicitis. If the special examinations I have described are carried out correctly the parietal location of the symptoms is easily recognized, but there always exists the possibility in any individual case that the parietal symptoms may mask the existence of an underlying true appendicitis. At the present time I know of no infallible method of excluding the possibility of true appendicitis underlying an acute parietal neuralgia. During the period in which I was attaining my present knowledge of pseudoappendicitis I did many appendectomies on patients in whom all the demonstrable symptoms were those of parietal neuralgia, and in none of them did I find an acutely diseased appendix at operation nor did the pathologist report anything other than chronic changes. Aside from undue pressure on the part of skilled consultants, the main reason for my having operated upon cases presenting definite parietal symptoms was a fear that an otherwise unaccountable fever and leukocytosis might be due to an underlying appendicitis. It is a very usual experience to encounter pseudoappendicitis cases without history or demonstrable evidence of any primary infection or following the apparently complete subsidence of a recent upper respiratory tract infection in which the temperature is 100° F. or slightly higher and the leukocytosis is 12,000 or 13,000. I have had several of these latter cases studied very carefully by expert internists and laryngologists to discover a lingering focus which might account for the fever and leukocytosis, but they have not been able to prove that it is in the nose, sinuses, throat, tonsils, larynx, bronchi or lungs. I suspect the paranasal sinuses are at fault.

Every patient with acute parietal symptoms on whom I have been induced to operate because of leukocytosis of varying degrees up to 15,000 failed to have acute appendicitis. All of the above were cases in which it was impossible to discover any focus responsible for the leukocytosis. I have abstained from operating upon dozens of similar cases, including 1 with an unexplained leukocytosis of 16,500, and in but 1 case did subsequent operation prove necessary. That patient was admitted during the active stage of an acute tonsillitis. She was a young child who could not speak English, hence the results of the tests were not reliable. Her abdominal symptoms were only a part of more generalized pain and tenderness which involved every part of the body surface. Several similar cases in young children cleared up without appendectomy, but this one required operation on the fourth day for a suppurative appendicitis from which she recovered. I now confidently await a favorable outcome in cases of acute parietal neuralgia in which the leukocytosis is 14,000 or less—even if the cause of the latter is not demonstrable elsewhere—and there are no other signs pointing to the appendix. The differential leukocyte count has not proven helpful in distinguishing between true and false appendicitis.

I had hoped to find that vomiting was limited to true appendi-

citis, but operation upon a few cases in which this symptom was present promptly demonstrated that it may occur in pseudoappendicitis. Nausea, without vomiting, is often present in pseudoappendicitis. My observations on vomiting indicate that many clinicians, not familiar with acute pseudoappendicitis, are wrong in laying great stress upon a positive history of vomiting in some earlier attack, as being a deciding factor in favor of true as opposed to false chronic appendicitis.

As I have previously explained, palpation tenderness is less marked over tense muscles—due to elimination of peritoneal tenderness—than over relaxed muscles. When this difference in tenderness is unusually pronounced there is always the fear that the large fraction of total palpation tenderness eliminated by tensing the muscles is due to a true appendix lesion. In the most extreme case of this kind which I have seen there was approximately only a tenth as much palpation tenderness over the tensed muscles as over the relaxed muscles, and the patient had a temperature of 100° F., a leukocytosis of 12,000 and frank symptoms of parietal neuralgia. Because of uncertainty as to whether the missing nine-tenths tenderness was entirely peritoneal or largely appendiceal in origin, it was decided to operate. Both grossly and microscopically the appendix was free from "acute" changes, but did exhibit "chronic" changes. Fortunately the peritoneal tenderness seldom exceeds half the total parietal tenderness in acute pseudoappendicitis. Excessive tenderness of the peritoneum was present in another recent case in which the parietal symptoms were very obvious and in which a leukocytosis of 14,000 of unexplained origin was found in a pupil nurse who gave a negative history of antecedent respiratory infection. Palpation over the ascending colon on two successive days did not cause any distress on the left side, but repeatedly brought forth complaints of increased pain in the appendiceal region. I became greatly interested in this patient's positive Rovsig's sign for appendicitis, as I thought it might prove a means of differentiation between true and false appendicitis. Believing that the right twelfth intercostal nerve was mainly at fault in this patient, I injected it with novocain, thereby hoping to eliminate the major part of the parietal tenderness, after which I could reapply the Rovsig test. My injection did not affect the parietal tenderness, due, as I now believe, to her tenderness having been caused by the eleventh instead of the twelfth intercostal. The gross and microscopic findings in the excised appendix were those of chronic changes only. It, therefore, seems probable in her case that the positive reaction to the Rovsig test was caused by the gas-distended cecum pressing against the hypersensitive parietal peritoneum. In one other unoperated case in which all other tests pointed to parietal trouble only, the Rovsig test was also positive. I have tested the Rovsig sign in only a few recent

cases of pseudoappendicitis, but I believe that it may be positive in both true and false appendicitis. I have not tried Bastedo's test of distending the cecum by pumping air into the rectum, but I assume it would give the same results as the Rovsig test. I also believe it is possible that both Rovsig's and Bastedo's tests may give a positive reaction simply from overdistention of the cecum in the absence of both appendicitis and neuralgia.

I have not made any attempts at injection of intercostal nerves with anesthetic solutions for the purpose of differentiating between parietal and appendiceal tenderness, but I think it will prove of value in certain cases. In this connection I was interested in a recent "aphorism" by Brandt, chief of the Oslo (Norway) Clinic, in which he asks a pointed question as to how many appendectomies are performed to cure neuralgia of the perforating branch of the right iliohypogastric nerve due to its "point douloureux" corresponding with the so-called McBurney's point. He finds that the paravertebral injection of 1 cc. of 50 per cent aqueous solution of antipyrin at its intervertebral foramen of exit almost always cures neuralgia of this nerve. Brandt also advises that "les points douloureux" and rheumatism of the abdominal wall should be considered before doing a laparotomy for intraperitoneal pains.

My experience with the Rovsig test led me to try Meltzer's method of palpation of the appendix over the iliopsoas muscle, While the latter is made tense by active flexion of the thigh with knee extended. This test does help to differentiate appendicitis from certain other lesions, but it has thus far proven confusing to me in differentiating between true and false appendicitis. With forceful active flexion of the thigh, Meltzer's test will prove positive in cases in which all the tenderness is located in the anterior parietes. Unless great care is exercised in another modification of Meltzer's test, the tenderness of true appendicitis is apt to be confused with tenderness of the right sacroiliac joint.

In planning this article, I had hoped I could sidestep at this time any discussion of rigidity as a differential sign between true and false appendicitis, but that now seems impossible. I am exceedingly loath to admit that rigidity may be encountered in very exceptional cases of acute pseudoappendicitis, because I fear that even any such restricted admission may lead to the careless assumption that it is frequent, with the disastrous result that diagnosis and operation will be delayed in cases of true appendicitis I hope any future writers will exercise like caution in referring to the possible presence of rigidity in acute pseudoappendicitis.

The relatively very small percentage of cases of parietal neuralgia of the abdomen caused by basilar pneumonia or pleurisy may exhibit rigidity of the abdominal muscles. In the cases in which rigidity is found the parietal abdominal symptoms, including rigidity, are usually restricted to, or at least are most marked on,

the side on which the basilar pneumonia or pleurisy is present. Before making the above concession as to the occurrence of abdominal rigidity in pneumonia, I had hoped to have an opportunity at postmortem to test out the following theory which I think may prove to be the explanation for its presence in some cases of basilar pneumonia and its absence in upper respiratory-tract infections.

I have already indicated that it is the systemic toxemia of the upper tract infections that commonly cause the clinical picture of pseudoappendicitis including the neuralgia of the parietal abdominal nerves. In basilar pneumonia and pleurisy I believe systemic toxemia may play a part, but that the main effect is due to a more direct action upon the lower intercostal nerves on the same side. This direct action may be a local toxic effect or it may be due to an extension of inflammation into or around the trunks of the lower intercostal nerves. These nerves are separated from the pleura by the intervention only of the very thin intercostal fascia through which theoretically it is easily possible for the adjacent inflammation to extend and irritate the nerves by toxins or by inflammatory exudate in or around the nerve trunks. I think it highly probable that in many cases the rigidity encountered in true acute appendicitis or peritonitis is due to a similar extension of inflammation into the abdominal wall, especially posterior, causing irritation of intercostal nerves. Every observant surgeon is aware that peritonitis may cause edema external to the transversalis fascia, a membrane not unlike the intercostal fascia. The clinical manifestations of intercostal neuralgia are almost entirely confined to sensory disturbances, but it is easily understandable that a somewhat stronger irritant would cause motor disturbance as indicated by muscular rigidity. Whether or not the direct extension of the inflammation through the intercostal fascia from the pleura or through the transversalis fascia from the peritoneum does cause this stronger irritation of the intercostal nerves needs to be determined by further studies. In many cases, however, the neuralgia appears too early in the pneumonia for infiltration to have occurred.

Except in cases of basilar pleuropneumonia, I believe the policy of wisdom for the present is to assume that rigidity, even when parietal symptoms are clearly demonstrable, points directly to an intraäbdominal inflammation which may be located in the appendix or any other viscus.

The abdominal symptoms of basilar pleuropneumonia usually depart from the typical symptoms of the particular intraäbdominal lesion under suspicion. Often the symptoms are confined to the upper abdomen, and in those cases the diagnosis from appendicitis does not require serious consideration. Onset of symptoms with chill points toward the pneumonic form of pseudoappendicitis, and, but not definitely, away from true appendicitis. High fever, leukocytosis over 30,000 and rapid respirations contraindicate true

appendicitis, irrespective of the presence or absence of parietal abdominal tenderness, pain and rigidity, and always demand careful investigation above the diaphragm before establishing a diagnosis of appendicitis. The severity of constitutional symptoms of fever, tachycardia and leukocytosis, contrasted with the mildness of local symptoms of pain, tenderness and rigidity often furnish the clue which leads to the correct differential diagnosis between an existent pneumonic pseudoappendicitis and a possible true appendicitis. Abdominal symptoms may appear before signs are demonstrable in the lungs. I have delayed operation in several suspected cases to have the suspicion confirmed by the appearance of frank signs of pneumonia within twenty-four hours. In only one instance can I recall having encountered coëxistent pneumonia and acute appendicitis, and that was in a baby who had an appendiceal abscess many years ago.

Although abdominal rigidity is absent in acute pseudoappendicitis except in the pneumonic form, I have gained the impression that slight motor irritability was present in a few other cases as shown after palpation by a muscle displaying a transient spasm. Such cases, however, are infrequent, and, except for the pneumonic type, pseudoappendicitis can be regarded as being characterized by an absence of abdominal rigidity. Absence of rigidity, however, does not exclude true appendicitis, as muscular rigidity may be absent even in the most acute forms of appendicitis.

The decision not to operate, in the great majority of these acute pseudoappendicitis cases, does not entail any special anxiety on the surgeon, provided they are kept under observation by himself or a competent physician. Their symptoms in the first place are not violent, and because of the acute primary infection and toxemia being terminal, amelioration of fever, tachycardia, leukocytosis, pain and parietal tenderness commonly occur after one or two days' rest in bed. If the surgeon becomes unduly anxious at any time, he can operate, but he should be prepared to find nothing more alarming than a "chronic" appendix.

I have gained the impression that there is a considerable group of individuals, especially among the visceroptotics, in whom the intercostal nerves are irritated to a point short of giving frank symptoms. This group tends ultimately to develop chronic pseudoappendicitis, but before doing so they display a predisposition to attacks of acute, subacute and recurrent pseudoappendicitis from relatively slight causes, such as mild infections, hypodermic injections of vaccines, menstrual phenomena, active exercise, mild vertebral trauma and so forth. Patients who have right-handed pain only in the late afternoon or evening, or following a customary day's work, and are relieved by lying down, belong to this group, as do other patients who have learned that the wearing of an ordinary corset overcomes their having similar pains.

Recurrent attacks of pseudoappendicitis are common and they simulate recurrent appendicitis. I always want to see the patient during a recurrent attack in order to apply the various tests I have outlined for acute pseudoappendicitis before agreeing to remove the appendix. The more numerous the preceding attacks of abdominal symptoms, the more likely is the case to be pseudoappendicitis. In many women the recurrent attacks occur mainly at the menstrual period. Relapsing appendicitis is simulated by pseudoappendicitis of chronic form with acute exacerbations.

Pseudoappendicitis does not render the patient immune to true appendicitis, hence the nature of the past attacks is not necessarily a correct index as to the nature of the present attack.

Preoperative differentiation between true and false appendicitis can be made only at the time of the attack and only by the special tests which I have outlined. The basic and most important step in detecting pseudoappendicitis, as well as many other pseudoinflammations of the abdominal and pelvic viscera, is the comparison of the results obtained by palpation over the abdominal muscles when they are fully relaxed and when they are purposely held as tense as possible. All the other tests are helpful, but they occupy a definitely subsidiary position. The tense muscle test does not require hours of skilled investigation in an expensive laboratory. It is a simple clinical test that can be carried out in one minute at the bedside of any patient who is not mentally incompetent.

My present knowledge of pseudoappendicitis has been slowly and painfully acquired, and is by no means complete. For instance, I have not had the opportunity to study enough cases of late peritonitis to formulate definite views as to possible confusion that may result from it giving positive reactions in some cases to the tests I have described for parietal neuralgia. I have not experienced any such confusion as yet, but I fear I may encounter it in the future. For the present I want to emphasize that the diagnostician should not lay too much stress on the special tests when the diagnosis of diffuse or late peritonitis is under consideration. I do know that in several cases in which operation disclosed edema of the preperitoneal fat and even an edema through the transversalis and internal oblique muscles the voluntary tensing of muscles eliminated tenderness that was easily demonstrable through the involuntary rigidity in each instance. In none of the above cases was there any cutaneous hyperesthesia on pinching.

One of the strikingly helpful evidences of the value of the two-stage lax-tense muscle test is the striking manner in which it demonstates the subparietal location of true intraäbdominal tenderness, provided there is no overlying parietal tenderness. In the cases in which exquisite tenderness is found in an appendix or gall bladder with the muscles relaxed, voluntary tensing of the muscles will prevent brutal palpation eliciting any tenderness. Notwithstand-

ing all the preceding observations, I still believe it is possible for a peritonitis, either by systemic toxemia or by direct extension into the belly wall, to cause neuralgia of the intercostal nerves supplying the anterior parietes.

No one can realize more fully that I that the last word has not been written on pseudoappendicitis, either acute or chronic, but I trust that my incomplete observations will stimulate other clinicians to clarify this very hazy subject.

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REVIEWS.

TEXTBOOK OF BACTERIOLOGY. By WILLIAM W. FORD, M.D., Professor of Bacteriology, School of Hygiene and Public Health, Johns Hopkins University. Pp. 1069; 186 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $8.50.

As a textbook "intended primarily for the medical student and the medical bacteriologist" this volume attains an excellence worthy of a review of great length. While comprehensive, the work maintains brevity and conciseness throughout, without sacrificing important and informing detail. The impartial viewpoint of the author and the elimination of irrelevant discussions are noteworthy. Recent advances and new data have been judiciously used to bring the subject matter up to date.

Part I contains an adequate historical introduction and presents the essentials of bacteriological methods and technique. A chapter on taxonomy is a particularly happy innovation.

Part II is devoted to systematic bacteriology, containing a maximum of informative description in the space allotted. Some unnecessary space is wasted on relatively unimportant microorganisms.

Part III deals with the distribution of bacteria, infection and immunity and infectious organisms of undetermined character. The spirochetes are considered at some length and a discussion of the bacteriophage is assigned a separate chapter.

The press work is excellent, and the illustrations are largely prepared from free hand drawings to present graphically to the student details of structure and morphological variation. A well selected bibliography accompanies each subsection. H. S.

ANATOMICAL, PHYLOGENETICAL AND CLINICAL STUDIES OF THE CENTRAL NERVOUS SYSTEM. By B. BROUWER, M.D., Professor of Clinical Neurology, University of Amsterdam. Pp. 67; 16 illustrations. Baltimore: The Williams & Wilkins Company, 1927. Price, $2.50.

THESE lectures delivered at Johns Hopkins University by this distinguished authority include: I. Projection of the Retina in the Brain; II. Pathology of Sensibility; III. Significance of Philo-

genetic Studies for Neurologists. That the macula is exclusively located in the occipital pole is disproved by preservation of central vision after severance of the fibers leading from there to the central optic radiation, so that some fibers must end elsewhere. The author's investigations do not prove the existence of Head's two pathways—protopathic and epicritic sensibility. Under multiple sclerosis it is commented that the cortex of the forebrain may often be affected. N. Y.

THE RELIGION CALLED BEHAVIORISM. By LOUIS BERMAN, M.D. Pp. 153. New York: Boni & Liveright, 1927. Price, $1.75.

A SATIRICAL refutation of the charge that the writer is himself a Behaviorist. Satire detracts from scientific value, though its trenchant phraseology may aid through directing attention to the present chaotic state of psychology. The Gestalt theory of Dr. Köhler is regarded the most important contribution since Freud's advent. Gestalt is the German word for pattern or form but its psychologic interpretation is here inadequate. It reverts to the introspectionist school so that a perception includes a grouping, a design, a pattern whose properties and qualities constitute its *meaning*. Cover, title and text show a sustained effort for public approval. N. Y.

SEGREGATION AND AUTOGAMY IN BACTERIA: A CONTRIBUTION TO CELLULAR BIOLOGY. By F. H. STEWART, M.A., D.Sc., M.D., Major, Indian Medical Service (Retired). With 4 plates and 23 tables. Paper boards. Demy 8vo. Pp. 104. London: Adlard & Son, Limited, 1927. Price, 7s. 6d.

SOME new observations on bacterial variation, based on more than ten thousand cultures, are shown to be best interpreted by Mendel's principles. Evidence is presented that bacteria pass through a life-cycle, corresponding to that of protozoa, with alternating phases of asexual and sexual reproduction. Bacterial variation and mutation are shown to be comparable to similar phenomena in higher plants and animals; primary variations follow autogamy, but reversion takes place in the asexual phase.

H. S.

THE HEALTH OF THE CHILD OF SCHOOL AGE. By VARIOUS AUTHORS. Pp. 204. New York: Oxford University Press, American Branch, 1927. Price, $1.80.

A SERIES of ten lectures delivered before the Institute of Hygiene and evidently intended for a semi-lay audience, is presented in this

small volume. The chapters on dental hygiene, on diet in schools and on the prevention of nose and throat infections particularly impress the reviewer. In the chapter on infectious diseases the lecturer advocates early infection with measles, by intentional exposure, a point with which the reviewer must disagree. The same lecturer gives interesting rules governing the prediction of epidemics in institutions. J. S.

CITY HEALTH ADMINISTRATION. By CARL E. MCCOOMBS, M.D. Pp. 524. New York: The Macmillan Company, 1927.

THE book is divided into three parts: I. Municipal Health Functions; II. The Organization and Administration of Sickness Preventive Functions; III. The Organization and Administration of Sickness Treatment Functions.

Different types of municipal government are explained in reference to the health and welfare organization prevailing in each type, with illustrations from the conditions existing in a number of the larger municipalities in the United States.

The administrative relations of the preventive and curative health functions are discussed. In the majority of American cities municipal activities for sickness prevention only, or for both sickness prevention and treatment are carried out by independent departments.

The general characteristics of boards of health are explained, with criticism and suggestion on health board administration.

The duties of the health officer, the different classes of employees in a health organization, and the special training required for each are treated fully.

The author, a member of the staff of the New York Bureau of Municipal Research and Training School for Public Service, has based his discussions on personal experience and on the reports of commissions investigating phases of government in actual operation.

The book will be of great benefit to all persons connected with the administration of public health organizations. D. B.

A TEXTBOOK OF MEDICINE. By 130 AMERICAN AUTHORS; edited By RUSSELL L. CECIL, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical School, New York. Pp. 1500; illustrated. Philadelphia: W. B. Saunders Company, 1927. Price, $9.00.

BRIEFLY stated, a system of medicine in one volume. One hundred and thirty prominent American physicians have contributed

to the work. Not only are they preëminent in their particular fields, but most of them are teachers of medicine, cognizant of the students' needs and viewpoint, thus assuring both the authoritativeness of the subject matter and the excellence of its presentation. Each chapter is really a monograph, surprisingly complete for the space available, and with numerous references to original sources. Proper proportion has been maintained throughout. A truly remarkable book that can be highly recommended both to students and practitioners. R. K.

APPLIED BIOCHEMISTRY. By WITHROW MORSE, PH.D., Professor of Physiologic Chemistry and Toxicology, Jefferson Medical College, Philadelphia. Second edition; revised and reset with the coöperation of JOSEPH M. LOONEY, M.D., Assistant Professor of Physiologic Chemistry, Jefferson Medical College. Pp. 988; 272 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $7.00.

THE call for a new edition within eighteen months of the publication of the first is sufficient indication both of the success of this book and the rapid advance of the subject. Among the important developments now first included are: "The more modern concepts in physical chemical physiology, such as the theory of the nucleus of the atom, the concept of activity, oxidation-reduction phenomena and methods, especially of the quinhydron electrode, the molecular weights of proteids, revision of the amino-acid content of proteids, more exact analytical procedures, such as methods for amino acids; the exact, rapid and convenient methods devised by Van Slyke for manometric determinations . . . a modern scheme for analysis of urinary calculi . . ." E. K.

DIE KLINIK DER BÖSARTIGEN GESCHWÜLTSTE. By PAUL ZWEIFEL, Director of the Obstetric-Gynecologic Clinic, University of Leipzig, and ERWIN PAYR, Director of the Surgical Clinic, University of Leipzig. Three volumes. Pp. 2310; 780 illustrations. Leipzig: S. Hirzel, 1924–1927. Price about $42.00 unbound; $50.00 bound.

IF it were necessary to read, mark, learn and inwardly digest these three massive volumes before writing a review, it would appear much too late to be of use to our readers. Fortunately, a much shorter perusal convinces one that a great work has been produced by German surgery. Though the treatment is mainly clinical and the authors mostly surgeons, the fundamental aspects of

oncology have been well presented, especially in Borst's opening article, and the scientific point of view consistently maintained. For anyone in medicine such a book is a profitable pleasure; for a scientific surgeon, a necessity.

In the first volume (860 pages and index) the general pathology of malignant neoplasms is followed by chapters on the special oncology of the skin, nervous system, eye, ear, nose, throat, larynx, jaw, tongue and mouth, salivary glands, thyroid, parathyroid, carotid body and branchiogenic tumors. In the second volume (740 pages and index) the cancers of thoracic and abdominal viscera, the male genitalia, skeleton and extremities are treated and in the third 630 pages and index) the breast and female genitalia are discussed with special sections on the radiation and vaccine treatments of cancer. As a reference book on an important and complex subject, it should remain the standard for as long as any such book can remain a standard in a rapidly advancing subject. E. K.

PRACTICAL BACTERIOLOGY, BLOOD WORK, PARASITOLOGY. By E. R. STITT, A.B., PH.G., M.D., SC.D., LL.D., Rear Admiral, Medical Corps and Surgeon-General, U. S. Navy. Eighth edition. Pp. 837; 211 illustrations. Philadelphia: P. Blakiston's Son & Co., 1927. Price, $6.00.

EACH new edition of this book revives one's astonishment that so much useful information can be brought into such small space, even though one realizes that the greatest care has been used to utilize each inch. One wonders how much more space would be saved if the diphthong were eliminated from all words including the root for "blood." In spite of this care, about one hundred pages have been added, to include *inter alia*, a chapter on diagnosis of tooth infections, the Kahn test, recent changes in streptococcus pathology, hemorrhagic diseases, sickle-cell anemia, liver function tests, etc. E. K.

A TEXTBOOK OF THERAPEUTICS. By ARTHUR A. STEVENS, M.D., Professor of Applied Therapeutics in the University of Pennsylvania. Seventh edition. Pp. 758. Philadelphia: W. B. Saunders Company, 1927. Price, $6.50.

"MUCH new matter has been added . . . ; many sections have been entirely rewritten." An important advantage in the new edition is its conformance to the tenth decennial revision of the U. S. Pharmacopœia (January, 1926). Some twenty-three new and important remedial measures have been added. E. K.

BOOKS RECEIVED.

Surgery: Its Principles and Practice. By ASTLEY P. C. ASHHURST, A.B., M.D., F.A.C.S. Third edition. Pp. 1179, 1061 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $10.00. (To be reviewed later.)

Surgical Diseases of the Gall-bladder, Liver and Pancreas and their Treatment. By MOSES BEHREND, A.M., M.D., F.A.C.S. Pp. 278, 101 illustrations. Philadelphia: F. A. Davis Company, 1927. (To be reviewed later.)

Nomogenesis or Evolution Determined by Law. By LEO S. BERG, D.Sc. Translated from the Russian by J. M. ROSTOVTSOW. Pp. 477, 33 illustrations. New York: Oxford University Press, American Branch, 1927. Price, $10.00. (To be reviewed later.)

Compendium of Regional Diagnosis in Affections of The Brain and Spinal Cord. By ROBERT BING. Third edition. Pp. 204, 102 illustrations. St. Louis: C. V. Mosby Company, 1927. Price, $6.00. (To be reviewed later.)

Physical Diagnosis. By RICHARD C. CABOT, M.D. Ninth edition. Pp. 536, 285 illustrations. New York: William Wood & Co., 1927. (To be reviewed later.)

Cancer Control. Report of an International Symposium held under the auspices of the American Society for the Control of Cancer. Pp. 336. Chicago: Surgical Publishing Company, 1927. (To be reviewed later.)

Affections of the Stomach. By BURRILL B. CROHN, M.D. Pp. 902, 361 illustrations. Philadelphia: W. B. Saunders Company, 1927. Price, $10.00. (To be reviewed later.)

A Manual of Materia Medica and Pharmacology. By DAVID M. R. CULBRETH, PH.G., M.D. Seventh edition. Pp. 1046, 197 illustrations. Philadelphia: Lea & Febiger, 1927. Price, $8.00. (To be reviewed later.)

Fistula of the Anus and Rectum. By CHARLES JOHN DRUECK, M.D., F.A.C.S. Pp. 318, 66 illustrations. Philadelphia: F. A. Davis Company, 1927. Price, $3.50. (To be reviewed later.)

Textbook of Psychiatry. By D. K. HENDERSON, M.D., F.R.F.P.S. and R. D. GILLESPIE, M.D., D.P.M. Pp. 520. New York: Oxford University Press, American Branch, 1927. Price, $5.50. (To be reviewed later.)

Textbook of Physiology. By WILLIAM H. HOWELL, PH.D., M.D., Sc.D., LL.D. Tenth edition. Pp. 1081, 308 illustrations. Philadelphia: W. B. Saunders Company, 1927. (To be reviewed later.)

Mental Handicaps in Golf. By THEO. B. HYSLOP, M.D., F.R.S.E. Pp. 112. Baltimore: Williams & Wilkins Company, 1927. Price, $1.50. (To be reviewed later.)

Ker's Manual of Fevers. Revised by CLAUDE RUNDLE. Third edition. Pp. 346, 15 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

The Medical Department of the United States Army in the World War. Volume II. Administration American Expeditionary Forces. Pp. 1123, 165 illustrations. Washington: U. S. Government Printing Office, 1927. (To be reviewed later.)

Osler's Modern Medicine, Volume V. Reëdited by THOMAS MCCRAE, M.D. Pp. 948, illustrated. Philadelphia: Lea & Febiger, 1927. Price, $9.00. (To be reviewed later.)

Progressive Medicine. Volume III, September, 1927. Edited by HOBART A. HARE, M.D., LL.D. Pp. 320. Philadelphia: Lea & Febiger, 1927.

Therapeutic Malaria. By G. DEM. RUDOLF, M.R.C.S., D.P.H. Pp. 223, 55 illustrations. New York: Oxford University Press, American Branch, 1927. Price, $3.85. (To be reviewed later.)

Hypnosis. Monograph Series No. 46. By PROF. PAUL SCHILDER, M.D., PH.D. and DR. OTTO KAUDERS. Pp. 118. Nervous and Mental Disease Publishing Company, 1927. (To be reviewed later.)

The Thomas Splint. By MEURICE SINCLAIR, C.M.G., M.B., CH.B. Pp. 168, 123 illustrations. New York: Oxford University Press, American Branch, 1927. Price, $4.50. (To be reviewed later.)

Surgical Clinics of North America. Brooklyn Hospital Number, August, 1927. Pp. 311, 168 illustrations. Philadelphia: W. B. Saunders Company, 1927.

Normal Midwifery for Midwives and Nurses. By G. W. THEOBALD, B.A., M.D., B.CHIR. (CAMB.). Pp. 258, 28 illustrations. New York: Oxford University Press, American Branch, 1927. (To be reviewed later.)

Clinical Diagnosis by Laboratory Methods. By JAMES CAMPBELL TODD, PH.B., M.D. and ARTHUR HAWLEY SANFORD, A.M., M.D. Sixth edition. Pp. 748, 346 illustrations. Philadelphia: W. B. Saunders Company, 1927. (To be reviewed later.)

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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AND

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PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Lobar Pneumonia: A Clinical and Bacteriologic Study of Two Thousand Typed Cases.—CECIL, BALDWIN and LARSEN (*Arch. Int. Med.*, 1927, **40**, 253) present a clinical, statistical study of 2000 consecutive patients from the wards of Bellevue Hospital, New York City. Their report is a long and complete survey of these patients, with particular reference to the clinical manifestations studied from the point of view of the several types of infection. Some of the studies show very little. On the other hand, some of them present findings which should be known by all clinicians; information, however, which can only be obtained by the proper typing of the pneumococci. This information would be of great value prognostically to the practitioner. For example, serious complications are twice as common in Type I infections as in other types. Type II and Type III pneumonia are twice as fatal as Type I and Type IV. Older people are particularly likely to be attacked by pneumococcus Type III. In Type II and Type IV there is a greater liability for multilobar involvement than in the other two types. An individual who has a positive blood culture has about two chances out of ten of surviving; if Type II and Type IV are responsible for the infection, one chance in ten. The young individual is much more prone to Type I infection and this same young individual is much more likely to survive than the older individual. The authors' figures, because they come from such a thoroughly well-studied series of cases, are of value. The duration of the disease in untreated patients who survived was found to average eight and four-fifths days. Fifty per cent of patients have a crisis. The death rate was higher in the winter months than in the summer months. The left lower lobe is the most frequent lobe involved, the right lower lobe coming next. If two lobes were involved it was usually the two lower lobes. Three lobes were rarely involved and four lobes almost never.

Mixed infections occur in about 25 per cent of the cases and the most frequent organism found in the mixed infections was the Bacillus influenzæ, the hemolytic streptococcus coming next in frequency but occurring in 75 per cent fewer cases than those infected with pneumococcus and Bacillus influenzæ. Systemic disease associated with pneumonia increases by 50 per cent the likelihood of a lethal termination. The greater the number of lobes involved, the more likely death is to occur.

SURGERY

UNDER THE CHARGE OF

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Primary Carcinoma of the Gall Bladder.—WEBBER (*Surg., Gynec. and Obst.*, 1927, **44**, 756) says that the grade of malignancy in 30 cases of primary carcinoma of the gall bladder, treated by cholecystectomy was studied to determine the existence of a relation between the length of life after operation and the grade of malignancy in the tumor removed. Twelve patients with carcinoma graded 2 or lower lived an average of two years and ten months. Fourteen patients with carcinoma graded 3 or higher lived an average of only forty-eight months. Two patients with carcinoma graded 2 are living; 1 has remained in good health six years and seven months and the other in fair health one year and one month. Of 12 tumors graded 2 or lower, 4 were found at operation associated with gross or microscopic evidence of extension or metastasis. Of 14 tumors graded 3 or higher, 13 were found at operation to be associated with similar evidence of extension or metastasis. In this group of cases the determination of the grade of malignancy through a study of the cell differentiation in a microscopic section of the tumor appeared to be a definite aid in estimating both the likelihood of metastasis and the relative length of the life of the patient after operation.

Thoughts on the Future of Thoracic Surgery in America.—MEYER (*Ann. Surg.*, 1927, **86**, 161) says that operative work within the chest is the same as in any other part of the body as far as surgical technique is concerned. With the application of the customary asepsis, such work is also equally safe if oxygen plus a volatile narcotic is added under pressure to the usual method of anesthesia. Injury of the thoracic viscera in accidents offers the most frequent indication for operation within the chest. Without prompt operation such injury often takes the patient's life in a few hours. For these reasons, it seems to be a matter of necessity that thoracic surgery, at least in its most important

and vital principles be added to the curriculum of the students in our medical colleges. Considering all points it is the author's belief that, in view of the favorable conditions under which thoracic surgery can now be undertaken it will not be long before it will become as much the general property of the profession as is the surgery of the abdomen and of other parts of the body at the present time.

PEDIATRICS

UNDER THE CHARGE OF

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Enlargement of the Spleen in Children.—BLEYER (*Am. J. Dis. Child.*, 1927, **34**, 176) observed that in three groups of cases of measles, comprising more than 500 cases, the spleen was found to be enlarged in 56 per cent. The appearance of the spleen at the height of the rash and its abrupt disappearance indicated that this reaction is related to the virus of the disease. No such reaction as was observed in measles occurred in the other common diseases of childhood. Active rickets showed enlarged spleens in about 1 case in 3. This was not due to an accompanying malnutrition. Mild rickets showed no reaction as to the size of the spleen. Syphilis was an uncommon cause of enlargement of the spleen in early life. Enlargement of the spleen was common among apparently healthy infants and is thus of little diagnostic help at this time. This is particularly true during the middle months of the first year of life, when it may be observed in about 1 case in 4. In the second year it was about half as common as in the first year.

Inorganic Blood Phosphate.—KOCH and CAHAN (*Am. J. Dis. Child.*, 1927, **34**, 187) found that the inorganic blood phosphate of rats six weeks old on the control diet was from 8 to 10 mg. This decreased rapidly to 6 or 7 mg., and then gradually to 4 or 5 mg. for the mature rats. Young rats fed the McCollum diet 3143 had an inorganic blood phosphate of from 2.3 to 3 mg., while the phosphorus values of mature animals on this diet were as low as 1.6 to 1.8 mg. Irradiation had no effect in raising the phosphate value of the young rats, but did tend to raise and maintain on a higher level the phosphate value of mature rats. The addition of cod liver oil to this diet raised the phosphate value in young rats to about twice the low values or from 4.3 to 5.4 mg. This was considerably below the normal values for rats of the same age. The addition of cod liver oil to the rachitic diet raised the blood phosphate values for mature rats to normal figures. Growing rats, receiving irradiated cholesterol, did not develop any signs of rickets. They had only slightly higher values for phosphate than those receiving the diet alone. Young rats, receiving nonirradiated cholesterol, had a similar phosphate concentration but developed rickets. The addition

of irradiated and nonirradiated cholesterol to mature rats again tended to keep the phosphate normal. Other groups to which irradiated oleic and palmitic acids and tyrosine were administered all had blood phosphate values of the same order as those receiving irradiated cholesterol. In spite of this all of these animals developed acute rickets. A return to the control diet after the rachitic diet raised the blood phosphate to the high level of young rats from 8 to 10 mg. The phosphorus concentration declined rather quickly, so that at the end of six weeks it was approximately normal. As a result of this study it is seen that while cod liver oil raises the blood phosphates to approximately normal, and direct irradiation of the animal and the feeding of irradiated cholesterol have some influence in raising blood phosphate, it is still possible to obtain a low phosphorus value and a low product of phosphorus times calcium in an animal which so far as roentgenograms and histologic examinations can demonstrate, shows a perfect calcification of the bones.

The Malnourished Child.—SAUER (*J. Am. Med. Assn.*, 1927, **89**, 931) analyzed the data of 30 consecutive children who were underweight. They ranged in age from five to twelve years and were treated by the individual method of intensive feeding. Most of the patients tired easily, were anemic and had poor posture. No child had been eating sufficient food; 24 had faulty food habits, such as improper food, eating between meals, especially sweets and iced foods or drinks. Twenty-six had been having insufficient rest. In 16 the cutaneous tuberculin tests were positive. These included 8 patients with bronchial gland involvement; 3 with tuberculous pleurisy; 2 with bone tuberculosis and 2 each with cervical gland and pulmonary tuberculosis. All but 2 were above the average height for their age and 20 were of the asthenic type. The thyroid gland was visibly enlarged in 9, 2 of whom had tachycardia and increased basal metabolic rates. Three had active, tardy rickets. The results as a whole are very gratifying. The few who failed to coöperate gained the least. Almost without exception, coincident with the weight increase there was a marked improvement in the pathologic condition. The results followed the removal of the underlying cause, and the eating of sufficient food of the proper kind and the establishment of ample rest, exercise and play.

Breast-feeding Problems.—MOORE and DENNIS (*J. Am. Med. Assn.*, 1927, **89**, 945) say that life, health and the proper development are all primarily affected by the nutrition of the baby. "The maintenance of an adequate breast supply through the normal period of nursing should be the paramount consideration in infant care. Whatever the disturbance may be that is giving rise to trouble, the physician should make every effort to discover the cause and to make the necessary dietetic and hygienic adjustments to correct it. The weaning of a baby does not require the attention of a physician, as anyone can do that, but to make possible the continuation of suckling is the duty of the doctor. The development of an adequate supply or the reëstablishment of an ample flow after premature weaning is perfectly possible if the physician and the mother are willing to make the required effort and practice the necessary perseverance. By using a breast-feeding

device, called the breast feeder, complemental feeding can be supplied while the baby is suckling at the breast. Parenteral and enteral diseases are more permanently cured by keeping the baby on the breast than by weaning it. A good rule to follow is that any mother who is well enough to care for her child is capable of nursing it.

Respiratory Anaphylaxis.—RATNER, JACKSON and GRUEHL (*Am. J. Dis. Child.*, 1927, **34**, 23) found that horse dander, when used in the dried state or in solution, can serve as an anaphylactogen. They presented a method for the preparation of the dry dander and for the extraction of an anaphylactogen from this material. They sensitized successfully guinea pigs by inhalation of dander. They induced shock by the inhalation of horse dander in guinea pigs previously sensitized by the injection of horse dander extract, and in some instances death was caused. Guinea pigs, sensitized by the inhalation of dry horse dander, when again subjected to the inhalation of dry horse dander after a suitable incubation period, showed respiratory symptoms of anaphylaxis. The symptoms noted in the last group were not different from those observed in the human being with asthma. Epinephrin diminished the symptoms in this same group in the same manner as it affects human beings with asthma. The nasal route can, under proper conditions, serve as the portal of entrance for foreign proteins, in the dry or liquid state, in the same way as a parenteral injection can do so. They believe that foreign proteins may enter the circulation through the nasopharynx. This opinion is based on the fact that death occurred after nasal inhalation almost as soon as after an intravenous injection. The swallowing of dry dander in capsules does not sensitize the animals. A state of anaphylaxis was produced in the guinea pig under conditions that would be regarded as natural or without the introduction of a substance by direct injection, and this fact supports the theory of acquired sensitization in the human being. The experimental data and the clinical evidence in the human being are so closely related as to suggest the point of view that anaphylaxis in the animal and asthma in the human subject are fundamentally the same. This particular type of anaphylaxis induced in the guinea pig by the inhalation of a dry animal emanation they call respiratory anaphylaxis as opposed to anaphylaxis induced by parenteral injections.

The Therapeutics of the Cardiac Child.—EPSTEIN (*Arch. Pediat.*, 1927, **44**, 576) reviews the therapeutics of the cardiac child at present as consisting of prevention of poverty, prevention of the infectious diseases and prevention of rheumatism; the radical treatment of any heart-damaging disease and the careful management of the already damaged heart. In endocarditis the treatment may be divided into three parts or periods of two weeks each. During the first period the child should be dosed with salicylates to saturation, for which purpose natural sodium salicylate is the best. Paregoric or codein may be given when indicated. For the next period guiacol carbonate or thiocol and quinin sulphate properly dispensed is recommended. While these drugs are not commonly used in endocarditis, they are valuable. Guiacol carbonate is as good a cardiac remedy as it is a pulmonary one. For the third period tonic treatment should be administered. Iron

citrate or saccharated ferrous carbonate, calcium glycerophosphate, strychnin and arsenic are most valuable. This therapeutic cycle should be repeated with weekly or two-weekly intervals of rest for an extended time. Prolonged care and a proper adjustment of the child to its future occupation is of the greatest importance.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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The Kahn Precipitation Test as Compared with the Wassermann.—The literature,[1] as investigated, interestingly interprets the value of the Kahn test as compared with that of the Wassermann, and a review is herewith compiled from the work of eleven investigators reporting during the years 1925, 1926 and 1927. A total of 355,885 tests was reported. The studies to day, however, have been concerned mostly with gross comparisons, by which I mean large numbers of tests without particular relation to the diagnosis or stage of the syphilitic infection. The technique used in the performance of the Kahn precipitation test as conducted by the various authors has been almost uniform. The Wassermann test, on the other hand, varied considerably as to technique, depending upon the individual modification of each laboratory. Considering this latter inconsistency, the interpretation of comparisons between various authors would lead one to expect a certain variation in the final results. Six facts cited as criteria for the superiority of one test over another stand out prominently. They are common to almost all the authors reporting and can be listed in the following order, in which they will be considered in this review: (1) Percentage of complete agreement; (2) disagreement; (3) sensitivity; (4) technical advantages; (5) simplicity; (6) sources of error. It must be kept in mind that this review does not take into consideration comparative results in relation to the stage of syphilis or of cases which have been diagnosed as syphilis. The tests were merely performed routinely upon specimens sent to the laboratories for that purpose. Comparing the reports pertaining to fact No. 1, that of the percentage of complete agreement, Walker obtained 86 per cent; Berry, Ey and DeLong, 95 per cent; Kahn, Kendrick and Landau, 97 per cent; Houghton, 93 per cent; Hull, 94.9 per cent; Kline and Young, 94.7 per cent. The variation is seen to be 11 per cent, with the lowest percentage of complete agreement at

86 and the highest at 97. Walker, who reports 86 per cent agreement, however, had a series of only 197 cases. Kahn, Kendrick and Landau, on the other hand, with a reported percentage of agreement of 97, had studied a series of 300,000 tests. Disagreement occurred in the following percentages: 14, 5, 3, 7, 5.1 and 5.3. This phase was admirably brought out by Greenbaum, who in an interesting study of 100 cases was able to compile 50 cases of diagnosed syphilis which gave positive Kahn tests and negative Wassermann tests, and a like number which gave positive Wassermann tests and negative Kahn tests. He suggested the use of both tests as necessary in the diagnosis of syphilis. Houghton, however, reported 76 positive Kahn reactions when the Wassermann was negative out of 40 cases, against 21 positive Wassermann reactions with negative Kahn tests out of 16 cases. The cases reported, according to Houghton, were undoubted syphilis. Walker reported 181 cases of diagnosed syphilis. All Kahn reactions were positive, whereas only 107 gave positive Wassermann reactions; 48 moderately positive reactions; 26 negative. Berry, Ey and DeLong cited 383 cases which were in the various stages of syphilis; 286 cases gave positive Kahn reactions and negative Wassermann reactions, while only 97 gave positive Wassermann and negative Kahn reactions. Relative agreement was reported in detail by Kahn and others from the study of 8661 cases of treated syphilis. Of this group only 66 per cent of complete agreement was noted, and the remaining 34 per cent was studied as to the comparative strength of reaction between the Kahn and the Wassermann. Seventy-nine per cent showed a stronger positive Kahn, while only 21 per cent showed a stronger positive Wassermann reaction. Sensitivity of such a serologic test was considered by the authors, all of whom agreed that the Kahn test is more sensitive than the Wassermann. Such sensitivity, however, has its disadvantages, according to such authors as Walker and Hopkins, who emphasized the dangers of too sensitive a test in that false positive reactions were more frequent. Walker further stated that the Kahn test could be rendered more sensitive or less sensitive just as the Wassermann could be, and in that way avoid the danger of false positives. Technical advantages, simplicity of performance, fewer sources of error and the absence of anticomplementary reactions were all facts in favor of the Kahn test.

REVIEW.

Berry, Ey, and DeLong: J. Am. Med. Assn., 1927, **88**, 1306.
Greenbaum: J. Am. Med. Assn., 1926, **86**, 1273.
Houghton, Hunter, and Cajigas: J. Am. Med. Assn., 1926, **88**, 1898.
Hopkins: J. Am. Med. Assn., 1927, **88**, 311.
Houghton: J. Am. Med. Assn., 1927, **88**, 719.
Hull: J. Am. Med. Assn., 1927, **88**, 1865.
Kahn: J. Am. Med. Assn., 1926, **87**, 2092.
Kahn, Kendrick, and Landau: J. Am. Med. Assn., 1927, **89**, 84.
Keim and Kahn: J. Am. Med. Assn., 1925, **84**, 881.
Kline and Young: J. Am. Med. Assn., 1926, **86**, 928.
Walker: J. Am. Med. Assn., 1927, **88**, 1468.

OBSTETRICS

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Amniotic Fluid as a Possible Factor in the Etiology of Eclampsia.—WARDEN (*Am. J. Obst. and Gynec.*, 1927, **14**, 292) gives us a study based on the amniotic fluid as related to eclampsia which appears to have been neglected in the study of the etiology of this disorder. He was unable to find any reference suggesting a relationship between the two in the literature. He refers to works of Williams and Bargen, who studied the chemistry of the amniotic fluid in relation to the uric acid content and that of the blood. He takes up several theories relative to the possibility of considerable amounts of amniotic fluid gaining entrance to the maternal blood stream and refers to the prompt relief and symptoms in eclampsia, when the amniotic fluid is drained away by rupture of the sac and the uterine cavity is relieved of its tension. Further, that the amniotic fluid may be found to be toxic and that the toxicity may be due to the accumulation within the amniotic sac of products of fetal metabolism. He tabulates his experimental work on rabbits and summarizes as an incomplete study that the intravenous injection of amniotic fluid into female rabbits occasionally produced convulsive seizures and death while other animals likewise treated did not seem to be seriously affected. That human amniotic fluid may contain material which, if injected into the blood stream could produce embolism, and further, the theory is suggested that eclampsia may be due to the sudden accidental injection of a considerable amount of amniotic fluid into the blood stream.

Uterosalpingography.—This article shows a decided advancement in methods of visualizing the cavity of the uterus and the Fallopian tubes. The method given by the author is outlined in detail. The materials used and injected into the uterine cavity through the cervix are the iodized oils. It is similar in many respects to the Rubin test or to the test offered by Rubin, which test offers resistance to the carbon monoxid-gas injections. JARCHO'S (*Surg., Gynec. and Obst.*, 1927, **45**, 129) method proves safer and more accurate when fluoroscopic and roentgenologic studies are made. In 1914 Carey tried the injections of collargol solution for the purpose of outlining the uterine cavity and the Fallopian tubes. Kennedy employed a 10 per cent solution of sodium bromid. Tussau and Mocquot, in 1925, used a suspension of bismuth, all for the same purpose, to demonstrate, if possible, abnormalities or irregularities in outline of the uterine cavity and tubal lumen.

Sicard and Forestier, in 1922, reported the use of lipiodol in 40 per cent combination of iodin with poppy-seed oil. Many others since that time have used in conjunction with Roentgen ray the iodized oils for injections, both in the uterine cavity, spinal canal and other regions of the body. The technique of the injection is precisely and clearly outlined, the roentgenograms and diagrammatic drawings in this article are beautifully executed and the distinct value of this technique in diagnosis. The advantages of the method regarding its safety and usefulness are unquestionable. First, in that it furnishes a valuable means of exact gynecological diagnosis in selected cases. In cases of sterility the patency of the tube and the localization of the occlusion can be clearly demonstrated, strict aseptic precautions must be taken and the author is firmly opposed to the test being made on ambulatory cases. Properly performed and proper interpretation of the test requires experience and if so accomplished should result in an accurate diagnosis. No manifestation of iodism has been seen in work accomplished.

GYNECOLOGY

UNDER THE CHARGE OF

AND

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Endometrioma of Labium Majus.—Although, thanks to Sampson's writings, we are beginning to recognize the frequent occurrence of ectopic endometrial growths in the pelvis, extrapelvic growths containing endometrial tissue are decidedly uncommon. HENRY (*Surg., Gynec. and Obst.*, 1927, **44**, 637) reports an interesting case in which a nodule removed from the upper pole of the right labium majus proved to contain such tissue. In a discussion too lengthy to review here he states that such growths have been regarded as "adenomyomata" of the round ligament and their origin assigned to: (1) Wolffian or Muellerian rests in the round ligament; (2) metaplasia and heterotopy of the peritoneal endothelium of the processus vaginalis or canal of Nuck; or (3) metaplasia of the endothelium of dilated blood or lymph vessels. Sampson, comparing the distribution of ectopic endometrial growths in general with that of the metastases of uterine and ovarian carcinomata, and recognizing their striking similarity, has concluded that the former may, and probably do, originate in the same way as the latter, namely: (1) By vascular (venous or lymphatic) dissemination of adult endometrial cells through the uterine veins or lymphatics or both; (2) by direct implantation of the same within the pelvis. Vascular dissemination probably accounts for the majority of endometrial growths of the round ligament, including its attachment in the labium majus, the lymphatic channel being a more direct one than

the venous. It is quite possible that endometrial cells may be implanted in labial excoriations during menstruation or decidual cells may be implanted if the labia are traumatized during delivery since it is known that both normal human endometrium and decidua can be implanted and will grow in abdominal scars.

Dilatation of the Ureter in the Female.—In order to throw more light on the subject of ureteral dilatation and ureteral strictures, which, it must be confessed, have had much light cast upon them from the direction of Baltimore, CARSON (*J. Urol.*, 1927, **18**, 61) has presented his findings in 115 consecutive autopsies on females. Ureteral dilatation was found in 31 cases, bilateral in 18, on the right side in 11 and on the left side in 2 cases. Forty-nine ureters were found dilated in 31 females with the kidney pelvis above dilated in 46 instances. Pregnancy is the most frequent cause of ureteral dilatation in women as shown in this series. Ureteral stricture, inflammatory in origin, was found in 4 cases, bilateral in 1 case and in 1 case there was a congenital ureteral stricture. It is interesting to note that of these 31 cases, 16 died during pregnancy or during the puerperium. Pelvic inflammation causing a periureteritis was found in 3 cases and a large myoma was the etiologic factor in 1 case. It seems to me that while this report shows that ureteral dilatation may be caused by pregnancy or other large abdominal tumors, which has been conceded by most investigators, it fails to show the presence of ureteral strictures as the causative factors as Hunner would have us believe.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Intraocular and Intracranial Pressure.—The experiments of FREMONT-SMITH and FORBES (*Arch. Neurol. and Psychiat.*, 1927, **18**, 550) show that, although the intracranial and intraocular pressures are not dependent on one another, changes of hydrostatic or of osmotic pressure induced in the blood produce a parallel change in pressure in the eye and in the cranium, or, in the words of Claud Bernard, parallel "response to variations in the internal environment." These observations serve to emphasize again the similarity in the mechanism for the formation and for the absorption of the intraocular and intracranial fluids, and to indicate that these mechanisms are fundamental in the fluid exchange of the body.

A Case of Angioid Streaks of the Retina.—MORGAN (*Proc. Roy. Soc. Med., Sect. Ophthal.*, 1927, **20**, 41) reports the case of a patient, a male, aged thirty-nine years, who was first seen in August, 1925, when he

complained that straight lines were slightly dented when seen by the right eye. The vision was 6/6 in both eyes. Both fundi showed marked angioid streaks, peripheral patches of old choroidal scarring, and faint pigmentary changes at both maculæ, but no hemorrhages or exudata. The patient was seen again in October, 1926, when he had a vision of 6/60 in the right eye and 6/6 in the left. The right fundus showed an angioid streak passing through the macula, white patches of exudate around the macula resembling those seen in retinitis circinata, and minute punctate hemorrhages in the deeper layers of the retina. This is the point of interest in the case, as it supports the view that, even if the streaks are not vessels, they are associated with vascular disturbance in the deeper layers of the retina or choroid and are closely related to retinitis circinata and Coat's disease.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Conditions of the Eyeball Arising from Rhinopharyngeal Disease.—Illustrating with clinical data of selected cases various points in his discussion, LUEDDE (*Surg., Gynec. and Obst.*, 1927, **44**, 775) divides the conditions of the eyeball related to nasopharyngeal disease into two primary groups, external and internal. The latter group he further divides into: (*a*) Disordered ocular functions without demonstrable organic changes; (*b*) pathologic changes in the ocular tissues. As causes for ocular disorders of purely functional type, he enumerates retrobulbar pressure, reflex nerve impulses, vasomotor disturbances and toxins. In the organic group, the author calls attention to the fact that no ocular structure is immune to pathologic changes arising from the nasopharynx, there being no reason why any of the tissues of the eyeball should be exempt, inasmuch as—with the possible exception of the conjunctiva—their vascular and lymphatic supplies are identical. Hence such conditions as superficial and interstitial keratitis, iritis, cyclitis, choroiditis, hyalitis, cataract, retinitis and retinal periarteritis, phlebitis, papillitis, optic neuritis, neuroretinitis, retrobulbar neuritis and toxic optic atrophy may be caused by various lesions in the nasopharynx and paranasal sinuses. Even the "three great bugbears of ophthalmology—glaucoma, retinal detachment and sympathetic ophthalmia—" seem to have more than a casual relation to certain rhinopharyngeal diseases. There is no particular type in these ocular inflammatory processes that positively identifies them as being due to diseases of the nasopharynx. Although clinical familiarity with certain types of ocular lesions may suggest a rhinopharyngeal origin, the actual diagnosis can only be made by exclusion. As there are no reliable short cuts to a complete diagnosis which would determine the etiological factors, the author emphasizes that the "whole patient must be studied."

Studies of Fusiform Bacilli and Spirochetes. No. XIII. Fusospirochetal Abscess of the Tonsil.—Acute angina is the common manifestation of tonsillar infection caused by Bacillus fusiformis and Vincent's spirochetes, organisms which can be demonstrated in large numbers in smears made from the membrane. Actinomyces-like granules made up largely of these bacteria are harbored in about 30 per cent of persons. Ordinarily the presence of these granular masses excites little or no cellular reaction, although Davis has shown that a chronic inflammation may occur if the granules dilate the tonsillar crypts. In cultures the bacilli occur in 82 per cent of tonsils which do not present any distinct changes with the exception of hypertrophy. Continuing his investigations along these lines, PILOT (*Arch. Otolaryngol.*, 1927, **5**, 244) encountered only 3 instances where chronic tonsillar abscess harbored both fusiform bacilli and spirochetes, although numerous abscesses were found in the routine examination of many hundreds of tonsils. The striking feature of the fusospirochetal abscesses was their chronic inflammatory character with a tendency to necrosis and the production of a foul-smelling exudate. These tonsillar lesions resembled those observed in certain forms of pulmonary abscess and gangrene. In this connection the author mentions the occasional occurrence of fusospirochetal pulmonary infection following tonsillectomy. With the knowledge that the middle ear and the paranasal sinuses may also become infected with these organisms, which are morphologically similar to those seen about normal and diseased gums and tonsils, it would appear that the bacteria of the mouth, about the teeth and in the tonsillar crypts, were the sources of infection. In all the reported cases streptococci, in addition to the fusospirochetal anaërobes, were isolated from the abscesses.

RADIOLOGY

UNDER THE CHARGE OF

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Gastric Lymphoblastoma.—Eight cases of lymphoblastoma of the stomach are reported by HOLMES, DRESSER and CAMP (*Radiology*, 1927, **7**, 44). In 5 of the cases well-developed localized gastric tumors were present and in these the findings were: sluggish, irregular peristalsis, which did not pass over the region of the lesion; a filling defect in the antrum or pyloric third of the stomach, usually annular in type, and gastric stasis. The Roentgen appearance did not differ from that of carcinoma, and this was the diagnosis in all cases save one in which the patient was known to have generalized lymphoblastoma. In this case, Roentgen ray treatment caused the filling-defect to diminish markedly and the patient's general condition improved.

Radiation Treatment of Esophageal Cancer.—A review of the literature by MARCUS (*Am. J. Roent. and Rad. Therap.*, 1927, **17**, 637) shows that the results of treatment of cancer of the esophagus are most unsatisfactory as to cure. By combined Roentgen and radium therapy, palliation for as long as two, three and even five years may be obtained, with a relief of symptoms, a lessening of the stenosis, and in some cases a disappearance of the lesion as revealed by the esophagoscope. The principal difficulties consist of the inability to determine by examination the extent of the disease, also the difficulty of early diagnosis and the peculiar anatomic conditions. Accidents in the treatment occur with great regularity and frequency, Necrosis, hemorrhage and perforation with pulmonary involvement are the usual complications. It is important to realize the futility of attempting to cure lesions which are advanced. Important neighboring organs are involved early and only palliation should be attempted. An attempt to treat advanced cases by intraesophageal applications of radium will meet inevitably with failure and result in death from hemorrhage or perforation. External irradiation may give clinical improvement and retard the disease for some time. Gastrostomy is an essential part of the treatment. Future hope lies in early diagnosis and heavily filtered radium over a long period, employing external radiation as a palliative in more advanced cases.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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The Infantile Type of Family Amaurotic Idiocy.—LEINER and GOODHART (*Arch. Neurol. and Psychiat.*, 1927, **17**, 616) report 2 cases clinically typical of amaurotic family idiocy. The histologic picture differed somewhat from the classic type. These cases do not confirm Hassin's conclusion that the process is most pronounced in the optic thalamus. However, they did find in both cases typical blastodermic selectivity without a uniform segmental selectivity, in one case the cerebellum being more involved, in the other the cerebral hemisphere. Also systemic electivity varied somewhat. They conclude that in the entire group of infantile types of amaurotic family idiocy there are a variety of subgroups, the connecting links being ectodermal selectivity of different degrees of Schaeffer's type of cell degeneration.

The Endocrines in Epilepsy: A Histologic Study.—SCHOU and SUSMAN (*Brain*, 1927, **50**, 53) call attention to the very few endocrine studies that have been made in epilepsy. Six cases are studied. All

of the endocrine organs were not available in all the cases. However, fairly constant lesions are reported in certain of the organs studied. Perivascular necrosis was found in all the genital glands studied, but is not considered distinctive. A distinct lesion was found in all 4 thyroids examined. Two pairs of adrenals studied showed chronic inflammatory changes. Pars glandularis of the pituitary (4 studied) were enlarged, and there was a certain similarity between these and lesions in the adrenal medulla. Only 3 pancreatic glands were available, but these all showed acinar degeneration, interacinar fibrosis and extremely enlarged islets. The external parathyroids were enlarged in all cases. The authors wisely refrain from drawing conclusions.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Multiple Hemorrhagic Sarcoma of Kaposi.—MEYERS and JACOBSON (*Am. J. Path.*, 1927, **3**, 321) report a case of this rare disease in a male patient, aged eighty-two years. Only 10 cases with complete autopsies have been reported in the United States; all showed thoracic and abdominal metastases. Roentgen ray plates of the thorax of this case showed no evidence of lung involvement. The histologic picture of the tumor supports and favors the diagnosis of sarcoma, while, on the other hand, its slow progress to a fatal issue is in decided contrast to most cases of sarcoma. They believe that a careful histologic study of the lesions indicates that the condition is one of multiple hemangeomatosis with a fibrosarcomatous change in the stroma of many of the tumor nodules.

The Reticulum of the Lungs—Its Similarity in Blastomycosis to that in Tuberculosis.—MILLER (*Am. J. Path.*, 1927, **3**, 315) reports the study of the pulmonary reticulum in 2 cases of blastomycosis. In a previous article on the character of the pulmonary reticulum in the bronchopneumonias associated with tuberculous lesions, he found that each of the three types presented a characteristic picture when stained for reticulum (*The Harvey Lectures*, 1924, Ser. 20, p. 42). From his study of the blastomycotic cases he concludes that the growth and transformation of reticulum into collagenous tissue differ in no way in the tubercle of blastomycosis from that in the tubercles of tuberculosis. The identity of the lesions is only made apparent by the presence of the organisms. That is, that though the organisms differ, the lesions they produce cannot be differentiated when producing tubercles.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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(*Concluded from November issue*)

"*How Cold Should Smallpox Vaccine be Kept?* The colder the better; well below freezing if possible. Ice-box refrigeration is not cold enough for this purpose. Smallpox vaccine cannot be injured by freezing, as can serums and other vaccines. Even a whole day out of cold storage, in addition to the necessary transportation from the manufacturing laboratory, may produce detectable deterioration in potency. Smallpox vaccine which has been out of cold storage so that it gives only about 80 per cent or 90 per cent of successful vaccinations on previous unvaccinated individuals may be satisfactory in ordinary outbreaks of smallpox or in routine vaccinations, but in the presence of severe smallpox or when reactions of immunity are to be observed the vaccine should be obtained direct from the manufacturer and kept below freezing. In the presence of severe smallpox, when there is uncertainty as to the potency of the vaccine, vaccination should be performed at more than one site, at least an inch apart, preferably with vaccine from different sources. Batches differ in their keeping qualities, but in recent years smallpox vaccine has with uniformity been found to be satisfactory as it leaves the manufacturer."

"*How Often Should One be Vaccinated against Smallpox?* Ordinarily once in every five to ten years, so that a maximum protection is maintained without the inconvenience at any time of a reaction more severe than the immunity reaction, except for the original primary vaccinia. Vaccination of infants is attended with less general reaction and fewer complications than vaccination of older children, so that vaccination is advisable as soon after birth as practicable. Immunity afforded by vaccination is lost by different individuals at different rates. The ability to ward off an attack of smallpox may be compared to proficiency in a foreign language. Such proficiency may be first acquired during early life and lost gradually, more rapidly in some individuals than in others. Some individuals need to be vaccinated more often than once in five years to maintain full protection and always to secure as the result of such vaccination merely an immunity reaction. Others may be vaccinated less frequently than once in twenty years and still maintain high immunity. It is a good plan to be revaccinated whenever one can be assured of a fully potent virus being used, so that the resulting reaction can be interpreted with certainty as showing a definite grade of

immunity. On the basis of such a reaction, with the knowledge of the individual's previous vaccination history, one can often advise as to how frequently in the future that individual should be revaccinated. The chance of taking the disease varies with the intensity of exposure and with the severity of the strain of smallpox to which one is exposed, as well as with the individual susceptibility. Those health officers who are continually exposed may need more frequent vaccination than the public at large. There is some evidence to show that infants and members of the colored races tend to lose their immunity more rapidly than others. A primary vaccination with one successful revaccination, or even a single successful vaccination, will as a rule protect throughout life from the milder forms of smallpox, but this is far from being true in the severer outbreaks. Second attacks of smallpox are rare, but do occur. If there is danger of exposure to a severe form of smallpox all persons who have not been vaccinated within one year successfully, that is, with vaccine known to be of full potency, should be vaccinated."

"*What are the Contraindications to Vaccination?* In general, skin diseases, particularly eczema, are the only conditions which will justify school attendance and at the same time be contraindications to routine vaccination. This is on account of the danger of diffuse vaccinia from carrying the vaccine into the open lesions of the skin disease, or the danger of contaminating the vaccination site if the skin lesions are purulent. Patients with such diseases as tuberculosis are in no wise harmed by properly performed vaccination. Acute infectious diseases may cause a vaccination 'take' to be delayed or atypical, but are not in themselves contraindications in case of possible exposure to smallpox. There is a curious relation in leprosy which tends to cause the lighting up of leprous lesions during the course of the vaccination, but which may promote more rapid healing thereafter. Serious lymphomatous diseases, including lymphatic leukemia, may be made worse by vaccination."

"*Will a Nonimmunized Person Contract Smallpox if Exposed to the Disease?* By no means uniformly. Exposure to smallpox, especially to the milder forms, without contracting the disease frequently occurs and is no definite evidence of immunity. The number of cases of smallpox among the unprotected persons in contact with patients suffering from the disease is very much less than 100 per cent."

"*Does the Failure of a Vaccination to 'Take' Indicate Protection?* No. Differences in skin receptivity may occur independently of the condition of the individual as regards true immunity. For example, very young infants are not as easily vaccinated as older children, yet they are susceptible to smallpox and when successfully vaccinated give a typical vaccinia. Some individuals may be resistant, in the same way, to a lot of vaccine which gives 'takes' generally in other individuals, but are not immune against smallpox when exposed, nor against vaccination when a fully potent lot of vaccine is used."

"*How Long After Exposure to Smallpox is it Worth While to be Vaccinated in Order to Hope that the Attack May be Warded off?* In some smallpox hospitals every person is vaccinated on admission, to guard against the danger from exposure in case of error in diagnosis. Successful vaccination performed on the day of exposure will almost always give complete protection against the smallpox attack, and vaccination

up to a few days before the onset at least makes the attack milder than it would otherwise have been. Vaccination during the few days before onset will allow the vaccination and smallpox eruption to develop simultaneously without either influencing the other."

"*What are the Most Important Points in the Diagnosis of Smallpox?* The diagnosis of smallpox may in some cases be difficult for the most experienced, but in order of their importance the most important diagnostic points are the distribution of the eruption, the individual lesions, the course of the disease, and inoculation tests. Of these four points the first two are of especial value because they are immediately available at first inspection of the patient. On account of its contagiousness smallpox should be diagnosed as promptly and as certainly as possible. The characteristics of the distribution are the most uniformly valuable of all the criteria of diagnosis, and are useful at almost any stage and in almost any case. The usual *distribution* of the smallpox eruption, general and in detail, and the character of the individual *lesion*, are shown by the following table (modified from T. F. Ricketts) of differences between the smallpox eruption and the chickenpox eruption:

SMALLPOX	CHICKENPOX
(*a*) Favors prominences, extensor surfaces, and surfaces exposed to irritation; tends to avoid protected surfaces, flexures and depressions.	(*a*) Is distributed indifferently in general, though not infrequently the eruption is especially thick over some particular area of the skin where there has been irritation.
(*b*) The forearms and wrists have a thicker eruption than the upper arms.	(*b*) The proximal part of the limbs have more of the eruption than the distal.
(*c*) Most abundant on face, most scanty on abdomen and chest.	(*c*) The abdomen and chest are covered as thickly as the face, or more thickly.
(*d*) More abundant on the back than on the abdomen.	(*d*) The abdomen has as many lesions as the back.
(*e*) More abundant on the shoulders than across the loins, and on the chest than on the abdomen.	(*e*) The distribution is indifferent as regards these regions.
(*f*) The eruption favors the limbs and generally the arms next to the face.	(*f*) Tends to avoid the limbs.
(*g*) Except when modified naturally or by previous vaccination, the lesions are deep-seated and have an infiltrated base.	(*g*) Unless they have become infected, the solitary lesions on the more protected parts of the body are superficial and the base is not infiltrated, so that the entire lesion tends to collapse on pressure.
(*h*) The solitary lesions on the more protected parts of the body are generally circular in outline.	(*h*) The lesions frequently have an irregular outline; when they lie near a flexure they are apt to be oval or elongated.
(*i*) The lesions tend to be all of the same sort at the same time, or if they are different, the smaller the lesion and the nearer it lies to the face the more advanced in development it should appear to be. In cases of modified smallpox the lesions are likely to vary greatly in size.	(*i*) Lesions at various stages of development may be found simultaneously, irrespective of their location or size.

The above description applies solely to the lesions of the characteristic eruption of smallpox, which go through the stages of papule, vesicle,

pustule, crust and scar, and not to the early rashes, erythematous or purpuric, which are seen rarely during the febrile stage preceding the real smallpox eruption, and which may in the most severe toxic cases constitute the only eruption prior to death."

"*What Effect Does Previous Vaccination have on Smallpox?* If recent, the vaccination will protect against the disease entirely. If the protection is not quite complete, on account of the vaccination having been performed too long before, the toxic early stages of the disease are the first to come out from under protection, and the resulting illness may have a fairly severe febrile onset for two or three days, though the following eruption be scanty and the indisposition trivial. The purpuric, uniformly fatal, form of smallpox is the most difficult to prevent by vaccination, and cases of this form, without a true smallpox eruption, may occur in persons with a fairly good vaccination history. The incidence of cases of this form depends on three factors—inherited predisposition, severity of the strain of smallpox, and immune status (remoteness of last vaccination).

"*Is There Another Contagious Eruptive Disease, Intermediate Between Smallpox and Chickenpox in Severity (Variously Called Alastrim, Milk Pox, Amaas, or Varioloid Varicella), which Might be Mistaken for Either of These Two Diseases?* No. Outbreaks of smallpox occur of all grades of severity, some with a mortality of 70 per cent among those attacked and some with a mortality of 0.01 per cent. Since 1896 a mild form has been increasingly prevalent in the United States and countries in communication with the United States, having a fatality of about 0.1 per cent among the unvaccinated."

"*Is Vaccination Alone a Sufficient Weapon for Fighting Smallpox?* No. Prompt recognition and rigid isolation of the cases, as well as the tracing out of 'contacts,' should also be carried out to stop the spread unless the outbreak is very mild and in thinly settled regions."

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 17, 1927

The Effect of Overbreathing and of Breathing Relatively High Concentration of CO_2 on the Urinary Excretion of Water and Chlorids.—G. E. SIMPSON (from the Department of Physiologic Chemistry, School of Medicine, University of Pennsylvania, Philadelphia). During sleep the urinary excretion of water and chlorids is low. The alveolar carbon dioxid tension is high and the pH of the blood low. These facts suggest the question: In general, do carbon dioxid tension of

the alveolar air and the associated factors in the blood such as pH bear a relation to the amount of water and chlorids excreted in the urine? If so, an increased excretion of water and chlorids would be expected not only on waking from sleep but also during overbreathing while the reverse would be expected when high concentrations of carbon dioxid were breathed. In experiments on overbreathing with men as the subjects, the excretion not only of water but also of chlorids was increased. In other experiments on dogs who breathed 4 to 50 per cent carbon dioxid in oxygen or air the excretion of water and chlorids was low during the carbon dioxid period. Thus, there seems to be a general relation in the sense mentioned above. An attempt is being made to determine whether the changes in water and chlorid excretion in any of these conditions is a result of a shift of water and chlorids from serum to corpuscles or the reverse. In the case of water excretion this is not so. In sleep, for instance, water content of the serum is high, although the volume of water excreted is low. As for chlorid excretion, in none of these conditions has any marked change in the chlorid content of the serum been demonstrated. During the carbon dioxid breathing there is a shift of water and chlorids from serum to cells but this is apparently accompanied by a flow of water and chlorids from tissues to serum.

The Effect of Electrolytes and Nonelectrolytes on the Rate of Osmosis in Living Cells.—M. McCutcheon and B. Lucke (from the Laboratory of Pathology, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole). Although permeability to water may be regarded as one of the most fundamental properties of living cells, the ease with which water enters or leaves the cell varies widely under different conditions. Thus, changes in the chemical composition of the fluid surrounding the cell greatly affect its permeability to water. The present communication is concerned with the effect of certain electrolytes and nonelectrolytes on this property. When a cell (in this case, the unfertilized sea urchin egg) is placed in dilute sea water, water enters the cell under the driving force of osmotic pressure, and the cell swells. The amount of swelling, and hence the amount of water entering the cell, can be measured at short intervals under the microscope. It has previously been shown[1] that this process follows approximately the equation $kt = 1n \frac{a}{a-x}$, in which a is the total volume change in the cell, x the volume change up to time t and k is the velocity constant. In this case k may be called the permeability constant, and used as a measure of permeability of the cell to water. In order to test the effect of electrolytes on permeability to water the cells were first placed in solutions of nonelectrolytes—dextrose, saccharose and glycocoll (the last, though not strictly speaking a nonelectrolyte, may be employed as such on account of its slight electrolytic dissociation). The solutions were all made of the same osmotic pressure as 40 per cent sea water (sea water, 40 parts; distilled water, 60 parts). The experiments were made at 12° C. (±0.5°). In these nonelectrolyte solutions the

[1] J. Gen. Physiol., 1926, **9**, 697 and 1927, **10**, 659.

same equation was found to hold as when the cells were in dilute sea water. The permeability constant, however, was about twice as great as in sea water of the same osmotic pressure, indicating a marked increase in permeability to water. Considering that this change might be due to absence of electrolytes, we sought to decrease permeability by adding small amounts of various electrolytes to hypotonic dextrose solution. We used chlorids of the cations occurring in sea water—the natural medium of the sea urchin egg. When enough NaCl or KCl was added to dextrose solution to give 0.01 molar concentration, the permeability constant was, as a rule, still further increased. But when the solution contained 0.01 molar or even as low as 0.0001 molar $CaCl_2$ or $MgCl_2$, the permeability constant was greatly decreased and was the same as in sea water of equal osmotic pressure. Thus evidence was obtained that Ca and Mg in the fluid about the cell have the effect of decreasing its permeability to water. That Na and K have an antagonistic effect to that of Ca and Mg was shown by adding, for example, both NaCl and $CaCl_2$ to dextrose solution. When these salts were added in appropriate ratio the resulting permeability constant was intermediate in value to those obtained when Na or Ca was present alone. By this method, therefore, we have been able to show quantitatively and directly that Na and K increase permeability of the cell to water, while Ca and Mg have the opposite effect.

Experiments Concerning the Question of Secretion of Phenolsulphonephthalein by the Renal Tubule.—A. N. RICHARDS and J. B. BARNWELL (from the Laboratory of Pharmacology of the University of Pennsylvania and the Laboratory of Zoöphysiology of the University of Copenhagen). Published in the Proceedings of the Royal Society, (B, 1927, **102**, 72).

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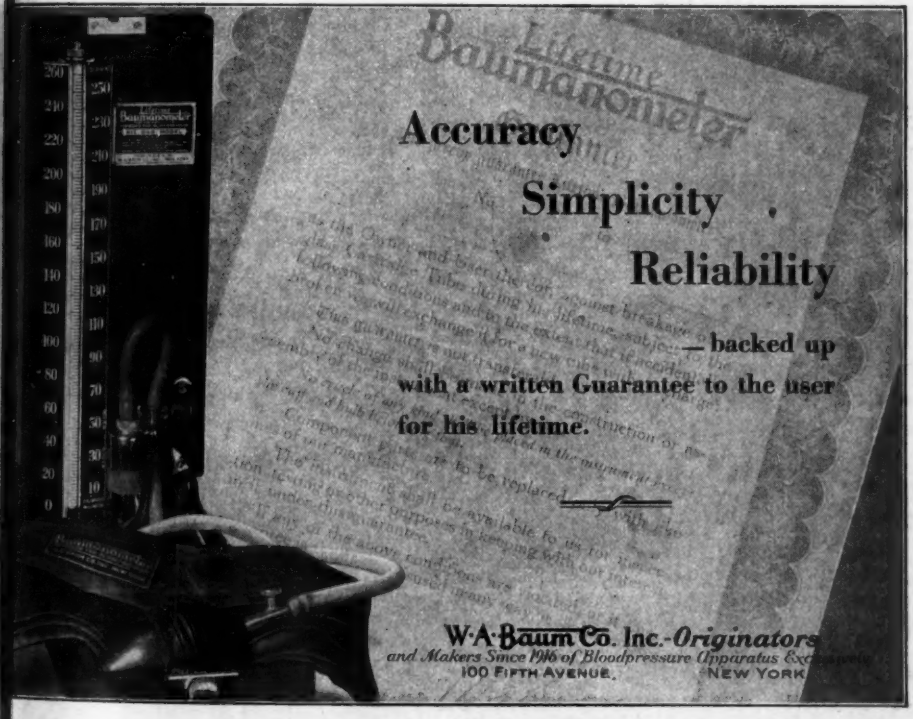
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